Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as post-exposure prophylaxis for Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2016638

This supplement contains the following items:

1. Protocol
    a. Original protocol, March 17, 2020
    b. Final protocol, April 24, 2020
    c. Summary of changes.

2. Original statistical analysis plan, May 6, 2020
    a. Clarifications May 24, 2020

Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial

Short Title: COVID19 PEP RCT

UMN IRB Number: STUDY00009267

FDA IND: 148257

ClinicalTrials.gov: NCT04308668

Principal Investigator: David R Boulware

Draft or Version Number: 1.0

17 **March 2020**

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This protocol will utilize a single institutional review board (IRB) registered with the Office of Human Research Protections (OHRP) and issued a Federal Wide Assurance (FWA). The research will be reviewed and approved by the IRB and will be subject to continuing review [45 CFR 46.103(b)].

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed:  Date: 3/17/2020

Name
Title

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience	
CFR	Code of Federal Regulations	
CONSORT	Consolidated Standards of Reporting Trials	
CFR	Code of Federal Regulations	
COVID19	coronavirus disease 2019	
SRS-CoV	SARS coronavirus	(i.e. circa 2003)
SARS-CoV-2	SARS coronavirus 2	(i.e. circa 2019)
CRF	Case Report Form	
CRO	Contract Research Organization	
DCC	Data Coordinating Center	
DHHS	Department of Health and Human Services	
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH	
DSMB	Data and Safety Monitoring Board	
eCRF	Electronic Case Report Form	
FDA	Food and Drug Administration	
FWA	Federalwide Assurance	
GCP	Good Clinical Practice	
HIPAA	Health Insurance Portability and Accountability Act	
ICF	Informed Consent Form	
ICH	International Conference on Harmonisation	
IDS	Investigational Drug Services	
IEC	Independent or Institutional Ethics Committee	
IND	Investigational New Drug Application	
IRB	Institutional Review Board	
MERS-CoV	Middle East respiratory syndrome coronavirus	
MOP	Manual of Procedures	
N	Number (typically refers to subjects)	
NIAID	National Institute of Allergy and Infectious Diseases, NIH	
NIH	National Institutes of Health	
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS	
OHRP	Office for Human Research Protections	
OHSR	Office for Human Subjects Research	
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS	
PCR	Polymerase chain reaction	
PHI	Protected Health Information	
PI	Principal Investigator	
SAE	Serious Adverse Event	
SOP	Standard Operating Procedure	
US	United States	
WHO	World Health Organization	

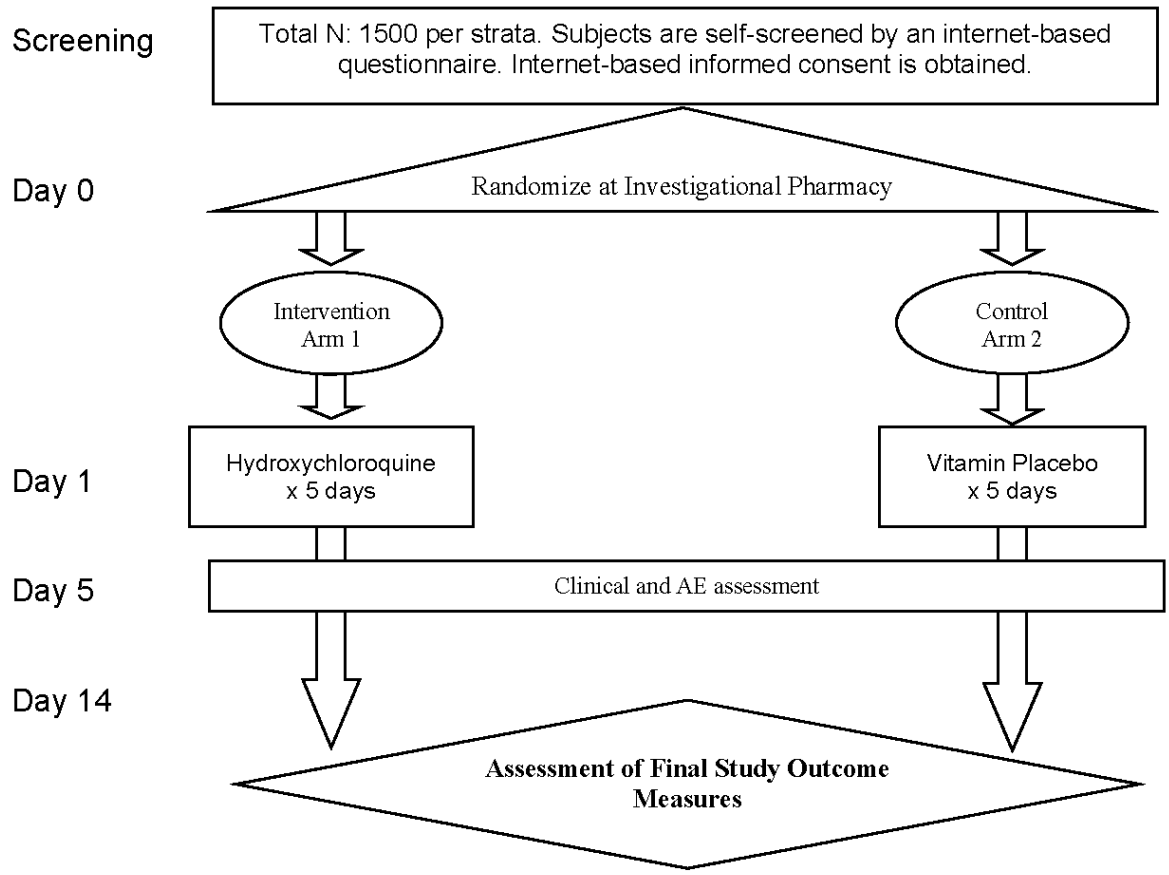
Summary

Full Title:	Post-exposure prophylaxis or Preemptive Therapy for coronavirus: A Pragmatic Randomized Clinical Trial
Short Title:	COVID19 PEP RCT
Clinical Phase:	III
Sponsor:	Investigator-Initiated Protocol, University of Minnesota
Principal Investigator:	David R Boulware, MD MPH
Accrual Ceiling	3000
Study Population	• Adult Household contacts or Healthcare workers exposed to persons with COVID-19 disease (n=1500), or • Non-hospitalized adults with symptomatic COVID19 disease (n=1500)
Objective	1) Test if post-exposure prophylaxis / early preemptive therapy with hydroxychloroquine can prevent progression development of symptomatic COVID19 disease after known exposure to the SARS-CoV2 virus. 2) Test if early therapy in non-hospitalized adults with symptomatic COVID-19 disease can prevent disease progression
Study Design	Double-blind, randomized clinical trial Internet-based trial driven by self-report. Study medicine delivered by FedEx to consented participants.
Intervention Arm:	Hydroxychloroquine 200mg tablet.

	800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days (5 days in total) *(This is a modified malaria dosing for hydroxychloroquine)*
Control Arm:	Placebo 4 tabs once, followed in 6 to 8 hours by 3 tabs, then 3 tabs once a day for 4 consecutive days (5 days in total)
Co-Primary Endpoints	● Incidence of COVID19 disease within 14 days among those who are asymptomatic. ● Ordinal Scale of COVID19 Disease maximum severity at day 14 among those who are symptomatic.
Secondary Endpoints	1. Incidence of Hospitalization for COVID-19 or death 2. Incidence of confirmed SARS-CoV-2 detection 3. Incidence of possible COVID19 symptoms 4. Incidence of all-cause study medicine discontinuation 5. Severity of symptoms at Day 5 and 14 6. Duration of Hospitalization 7. Cumulative incidence of time to negative PCR test (from time of PCR+)
Duration of Participation	● Recruitment and follow up will be internet-based. ● 14 days of active participation ● Up to 90 days follow up for those with COVID19 diagnosis to assess final outcome.
Inclusion Criteria	● Exposure to a COVID19 within 4 days, either as: ○ Healthcare worker, or ○ Household contact, or ○ Individual with COVID-19 disease confirmed by PCR+ or by compatible symptoms with exposure to known PCR+ case with <=4 days of symptoms. ● Age >=18 years of age ● Provision of Informed Consent
Exclusion Criteria	• Current hospitalization • Allergy to chloroquine or hydroxychloroquine • Prior retinal eye disease • Concurrent malignancy requiring chemotherapy • Known Chronic Kidney disease, Stage 4 or 5 or dialysis. • Known glucose-6 phosphate dehydrogenase (G-6-PD) deficiency. • Known Porphyria • Weight <40 kg

	• Current use of: hydroxychloroquine or cardiac medicines of: flecainide, amiodarone, digoxin, procainamide, or propafenone
Stratification	Randomization will be stratified by baseline status of COVID-19 disease vs. asymptomatic with exposure. Analyses will be separate for asymptomatic vs. symptomatic cohorts.
Statistical Assumptions	● 10% attack rate for close contracts (or 10% progression of disease to hospitalization among those symptomatic at entry) ● Comparison of Proportions by Fisher's Exact test for disease incidence; ● Comparison of ordinal scale of disease severity by proportional odds model ● N=621 sample per arm has 90% power to detect a 50% relative risk reduction (i.e. $\leq$5.0%) in disease incidence or 50% decrease in the ordinal disease severity (to $\leq$4.25% disease incidence and $\leq$1% hospitalization). ● 20% dropouts, inflates sample size to n=750 per arm

Schematic of Study Design:



For participants who develop symptomatic disease, they will be followed for up to 90 days to assess final outcome status.
Stratification is based on symptom status at baseline, 1500 per strata.

1 KEY ROLES

Individuals:

Principal Investigator: David R. Boulware MD, MPH, CTropMed

Co-Investigator: Sarah Lofgren, MD

Co-Investigator: Alison Galdys, MD

Co-Investigator: Matthew Pullen, MD

Co-Investigator: Radha Rajasingham, MD

Co-Investigator: Joshua Rhein, MD

Co-Investigator: Meghan Rothenberger, MD, CTropMed

Co-Investigator: Caleb Skipper, MD

Co-Investigator: William Stauffer, MD, MSPH, DTM&H

Medical Monitor: Mahsa Abassi, DO MPH

Pharmacologist: Melanie Nicol, PharmD, PhD

Biostatistician: Kathy H Hullsiek, PhD

Associate Statistician: Ananta Bangdiwala, MS

Associate Statistician: Nicole Engen, MS

Institution: Division of Infectious Diseases, Department of Medicine, University of Minnesota, Minneapolis, MN

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Significance of Research Question/Purpose:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rapidly emerging viral infection causing COVID19. The current strategy uses a public health model of identifying infected cases, isolation, and quarantine to stop transmission. Once exposed, observation is standard-of-care.

No effective therapy currently exists for treatment. The lack of effective therapy diminishes persons presenting post-exposure for self-quarantine. Having an effective post-exposure prophylaxis, even if only partially effective, may additionally create synergy for the public health strategy of case identification and isolation – if a safe prophylaxis is available.

People who develop COVID-19 disease generally develop signs and symptoms, including mild respiratory symptoms and fever, after an average of 5-6 days after exposure (i.e. mean incubation period). The range of the incubation period is between 1 to 14 days.[1]

Most people infected with the COVID-19 virus have mild disease and recover. Approximately 80% of laboratory-confirmed patients have had mild to moderate disease, which includes non-pneumonia and pneumonia cases, 14% have severe disease, and 6% are critically ill with respiratory failure, shock, and/or multiple organ dysfunction [1].

Preliminary Data:

Chloroquine has *in vitro* activity in cell lines against SARS-CoV and SARS-CoV2. In a Vero E6 cell line, the half-maximal effective concentration (EC50) activity of chloroquine was 1.13 μM against SARS-CoV2 [2]. Hydroxychloroquine is functionally equivalent as chloroquine.

Another compound under treatment trials, remdesivir (Gilead) had an EC50 of 0.77 μM [2]. Remdesivir (Gilead) is not FDA-approved and in limited quantities. Hydroxychloroquine is FDA-approved and globally is inexpensive. Chloroquine is no longer broadly available in the USA.

Existing Literature:

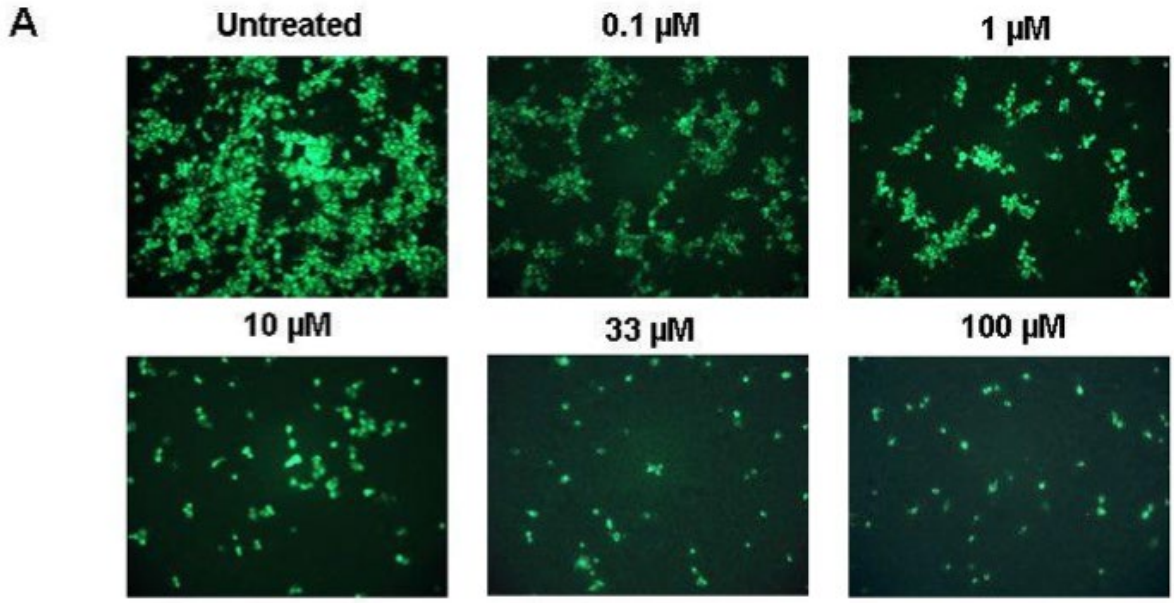
Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy is poorly understood as a gold standard randomized clinical trial has not been conducted.

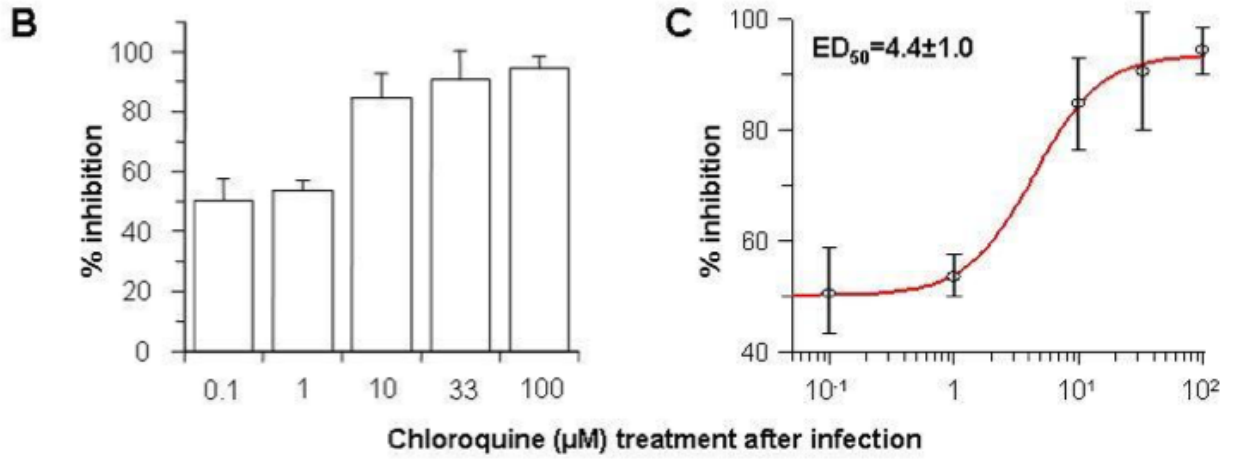
After the original 2003 SARS outbreak, screening of compounds was performed. The Special Pathogens Branch of the Division of Viral and Rickettsial Diseases at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia investigated chloroquine.

CDC investigators reported that post-infection chloroquine treatment was effective in vitro at preventing the spread of SARS-CoV infection in an in vitro cell-based system [3]. Vincent et al reported:

> "In order to investigate the antiviral properties of chloroquine on SARS-CoV after the initiation of infection, Vero E6 cells were infected with the virus and fresh medium supplemented with various concentrations of chloroquine was added immediately after virus adsorption. Infected cells were incubated for an additional 16–18 h, after which the presence of virus antigens was analyzed by indirect immunofluorescence analysis. When chloroquine was added after the initiation of infection, there was a dramatic dose-dependent decrease in the number of virus antigen-positive cells (**Fig. 2A**). As little as 0.1–1 μM chloroquine reduced the infection by 50% and up to 90–94% inhibition was observed with 33–100 μM concentrations (**Fig. 2B**). At concentrations of chloroquine in excess of 1 μM, only a small number of individual cells were initially infected, and the spread of the infection to adjacent cells was all but eliminated. A half-maximal inhibitory effect (EC50) was estimated to occur at 4.4 ± 1.0 μM chloroquine (**Fig. 2C**). These data clearly show that the addition of chloroquine can effectively reduce the establishment of infection and spread of SARS-CoV if the drug is added immediately following virus adsorption." [3]

Figure 2. Post-infection chloroquine treatment reduces SARS-CoV.





Vincent et al also reported: “Since we observed antiviral effects by chloroquine immediately after virus adsorption, we further extended the analysis by adding chloroquine 3 and 5 h after virus adsorption and examined for the presence of virus antigens after 20 h. We found that chloroquine was still significantly effective even when added 5 h after infection (Fig. 3); however, to obtain equivalent antiviral effect, a higher concentration of chloroquine was required if the drug was added 3 or 5 h after adsorption.” [3]

Further experiments demonstrated that chloroquine impaired the terminal glycosylation of angiotensin-converting enzyme-2 (ACE2) receptor, which is the binding site for the envelope spike glycoprotein of SARS-CoV and SAR-CoV2 [3].

Conversely, chloroquine did <u>not</u> have activity against Middle East respiratory syndrome coronavirus (MERS-CoV), which may be related to MERS binding to CD26 receptor protein [4].

In a March 9, 2020 publication, hydroxychloroquine was found to have greater activity than chloroquine [5. **The SARS-CoV-2 EC 50 values for hydroxychloroquine were 6.14 μM at 24 hours and 0.72 μM at 48 hours,** [5]. Conversely, chloroquine EC50 values were >100 μM at 24 hours and 18.01 μM at 48 hours [5]. This inhibition assay was performed with Vero cells using an infectious dose of 100 plaque forming units.

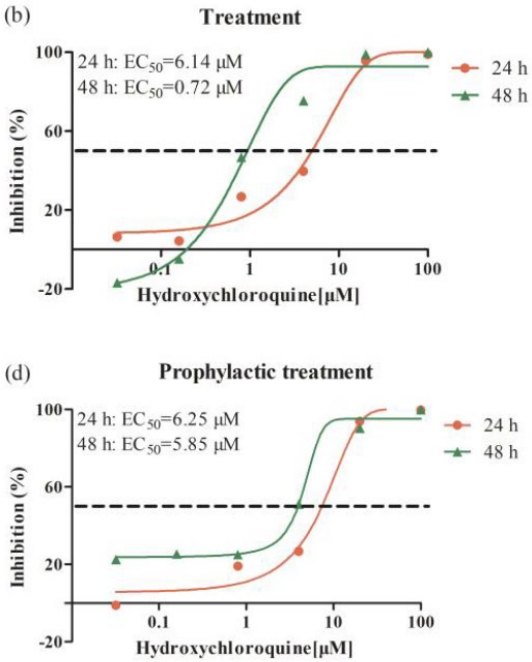


Figure 3 displays the antiviral activities of hydroxychloroquine for treatment or prophylaxis against SARS-CoV-2 *in vitro* [5].

2.2 Rationale

Current standard of care is observation and quarantine after exposure to COVID19.

As of March 6, 2020, the CDC estimates that the transmission of SARS-CoV2 after a U.S. household close contract is 10.5% (95%CI, 2.9 to 31.4%) [6]. Among all close contacts, the SARS-CoV2 transmission rate is estimated at 0.45% (95%CI, 0.12 to 1.6%) by the CDC. These estimates are based on monitoring of travel-associated COVID19 cases. Conversely, in a setting with community transmission, the secondary attack rate in China was 35% (95%CI, 27-44%) based on 48 transmissions among 137 persons in 9 index patients.

Chloroquine or Hydroxychloroquine may have antiviral effects against SARS-COV2 which may prevent COVID19 disease or early preemptive therapy may ameliorate disease severity. This trial will use a modification of standard malaria dosing of hydroxychloroquine to provide post-exposure prophylaxis / preemptive therapy.

Standard malaria treatment dosing is:

- 800mg once, then 400mg in 6-8 hours, then 400mg daily x 2 days (3 days in total).

We propose to dose for SARS-CoV-2 post-exposure prophylaxis at:

- 800mg once, then 600mg in 6-8 hours, then 600mg daily x 4 days (5 days in total).

The projected levels achieved will be approximately 4.4 μM which is at or above the half maximal effective concentration (EC50) where 50% viral inhibition would occur. A delayed start to prophylaxis will be occurring -- based on the intrinsic delay from the exposure to case notification to trial enrollment, and to receipt of the first medication dose. Thereby, higher doses may be necessary as seen in the CDC study [3]. Thus a malaria loading dose sequence will be used, but with higher daily doses thereafter to target reaching the above the EC50.

As the incubation period is 2-14 days with a mean incubation period of 5-6 days, we seek to deliver post-exposure prophylaxis by the morning of day 4 at the latest. (<=3 days is an inclusion criteria). We recognize this may turn “post-exposure prophylaxis” into more of a “preemptive therapy” for some subjects who rapidly develop disease after trial randomization. If hydroxychloroquine does not prevent disease for some, preemptive therapy may ameliorate the COVID19 disease severity. Attenuated disease may in turn be associated with reduced rates of transmission.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Short-term use of hydroxychloroquine is well-tolerated with a safe track record since 1955. The most common reported side effects include:

- headache, dizziness, ringing in your ears;
- nausea, vomiting, stomach pain;
- loss of appetite, weight loss;
- mood changes, feeling nervous or irritable;
- skin rash or itching; or.
- hair loss.

GI side effects are minimized when taken with a meal or with milk. Antacid medications should be spaced apart by at least 4 hours.

- Potential adverse effects by system, as listed on the FDA package insert:
  - **Eye**: “Chloroquine retinopathy” is a rate side-effect of chronic use after multiple years of use. This has not occurred with <1 year of continuous use.
  - **Dermatologic Reactions**: Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).
  - **Hematologic Reactions**: Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, anemia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).
  - **Gastrointestinal Reactions:** anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.
  - **Cardiac Reactions:** Long-term use (>1 year) has been associated with the development of cardiomyopathy and arrhythmias. Specifically, chronic use has been associated with a mean +25msec prolongation of the QT interval after a median use of 3.5 years in patients with autoimmune diseases. In a 2018 review of short term antimalarial treatment trials (n=1076 with chloroquine), no serious cardiac adverse events were reported among 35,548 participants [haeusler]
  - **Allergic Reactions**: Urticaria, angioedema, and bronchospasm have been reported
  - **CNS Reactions**: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia
  - **Miscellaneous Reactions:** Weight loss, lassitude, exacerbation or precipitation of porphyria and non-light-sensitive psoriasis. Possible Hypoglycemia in persons with diabetes

2.3.2 Known Potential Benefits

- There are no known benefits in humans for preemptive treatment.
- *In vitro* antiviral activity against SARS-CoV and SARS-CoV2 viruses.
- Chloroquine and Hydroxychloroquine have a long history of safe, effective use as an antimalarial, both acutely and long-term use.
- Chloroquine is being used therapeutically for severe COVID19 disease in China and Korea.
- Commonly used as a chronic medication for autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus).
- Recent studies have shown potential broad antiviral effects *in vitro* at dosages below currently recommended clinical dosing, reducing risk of potential adverse effects listed above.

3 OBJECTIVES

3.1 Study Objectives

To determine if post-exposure prophylaxis with hydroxychloroquine is effective at prevention of COVID19 disease or ameliorating disease severity.

3.2 Study Outcome Measures

3.2.1 Co-Primary Outcome Measures

- Incidence of COVID19 disease within 14 days (among those asymptomatic at baseline)
- Ordinal Scale of COVID19 Disease Severity
    - No illness
    - Illness with outpatient observation
    - Hospitalization (or post-hospital discharge)
    - Hospitalization with ICU stay or Death

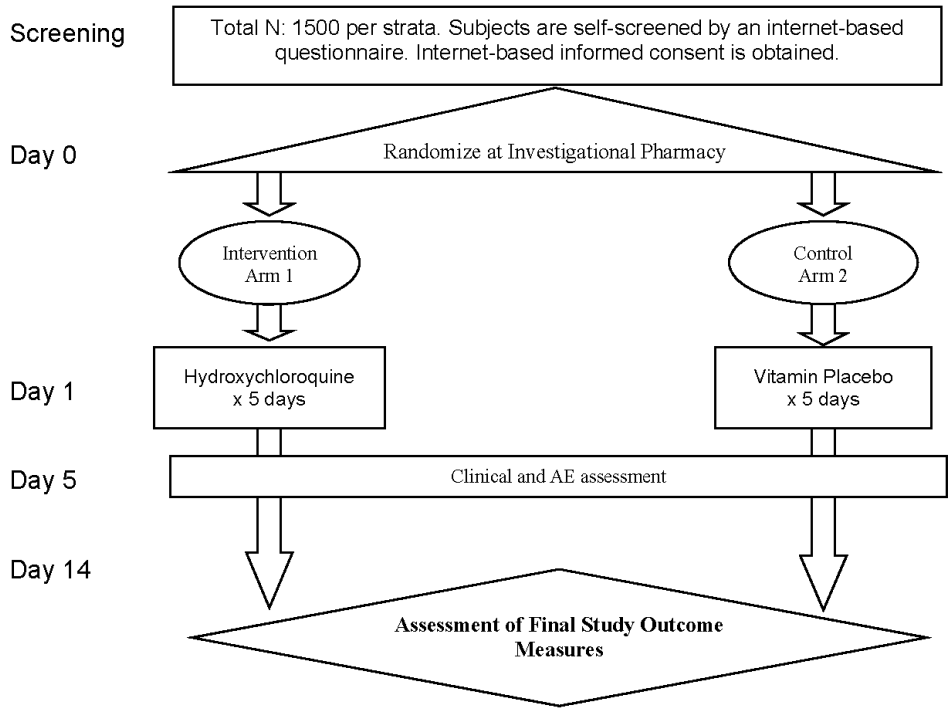
3.2.2 Secondary Outcome Measures

- Incidence of hospitalization or death
- Incidence of confirmed SARS-CoV-2 detection
- Incidence of symptoms compatible with COVID19 (possible disease)
- Incidence of all-cause study medicine discontinuation or withdrawal
- Symptom Severity on day 5 via visual analog scale
- Duration of hospitalization, among those hospitalized
- Cumulative incidence of time to PCR-negativity among those with a positive PCR test

Analysis will be stratified by baseline COVID-19 symptom/disease at enrollment.

Assessment of outcome measures will be primarily by self-report. As necessary, COVID19 disease will be verified from public health records, medical records, or death certificates.

4 STUDY DESIGN



There are two strata: 1) asymptomatic exposures; 2) symptomatic COVID-19 disease
Follow up will occur up to 90 days for those with symptomatic COVID-19 disease.

4.1 DESIGN

Randomized, double-blind clinical trial, parallel design

4.2 Study participant duration

- 14 days consisting of internet-based virtual visits
- For participants ill with COVID19 disease, observational follow up will extend to up to 90 days to assess final outcome status.
- Pregnant women have their fetal outcome assessed post-partum.

4.3 Study procedures

4.3.1 Screening

- Baseline screening for eligibility via self-administered questionnaire
- Informed consent

4.3.2 Randomization

- Participants will be randomized

- The investigational pharmacy will dispense masked study medicine (hydroxychloroquine or placebo)
- The study medicine will be sent to participants overnight via FedEx to arrive at approx. 10:30am.

4.3.3 Day 1 Virtual visit

- Verify receipt of study medicine
- Clinical status check-in
  - Begins taking study medicine (4 tabs), then 3 tabs in 6-8 hours, then daily. Query for SARS-CoV-2 testing
  - Query for symptom status
- Query for hospitalization or SAEs

4.3.4 Day 5 Virtual visit

- Clinical status check-in
- Assessment of adherence by self-report
- Completion of study medicine, which has a ~7 day half-life
  - Query for study medicine side effects since enrollment
  - Query for SARS-CoV-2 testing
  - Query for hospitalization or SAEs

4.3.5 Day 14 Virtual visit

- Clinical status check-in
  - Query for study medicine side effects since enrollment
  - Query for SARS-CoV-2 testing
  - Query for hospitalization or SAEs
- Query for pregnancy status
- Final outcome assessment

4.4 Individually identifiable health information: Name, date of birth, and phone number will be collected so as to prescribe study medication. Email addresses will be collected for communication. If participants are hospitalized, the hospitalization date will be collected.

4.5 Substudies (if applicable)

N/A

5 STUDY ENROLLMENT AND WITHDRAWAL

Participants will undergo screening via internet-based google forms. The screening and inclusion criteria will be based on self-report.

5.1 Subject Inclusion Criteria

- Exposure to a COVID19 case within 4 days as either:
    - Healthcare worker
    - Household contact

  OR
- Healthcare worker / household contact with symptomatic COVID19 disease with <u><=</u>4 days of symptoms) and:
    - Confirmed diagnosis with PCR+ SARS-CoV-2 or
    - Exposure to known PCR+ SARS-CoV-2 case within 14 days AND compatible symptoms of fever, cough, or shortness of breath (and no available testing for the individual)*
- >= 18 years of age
- Provision of informed consent

5.2 Subject Exclusion Criteria

- Current Hospitalization
- Contraindication or allergy to hydroxychloroquine
- Retinal eye disease
- Known glucose-6 phosphate dehydrogenase (G-6-PD) deficiency
- Known chronic kidney disease, stage 4 or 5 or receiving dialysis
- Known Porphyria
- Weight < 40 kg
- Current use of: hydroxychloroquine or cardiac medicines of: flecainide, Tambocor; amiodarone, Cordarone, Pacerone; digoxin or Digox, Digitek, Lanoxin; procainamide or Procan, Procanbid, propafenone, Rythmal)

Rationale for inclusion / exclusion criteria:

* As of 17 March 2020, testing is limited in many U.S. states and locales due to insufficient supplies. Thus, outpatient testing may not be available. A person with known exposure to a confirmed COVID-19 case with subsequent compatible symptoms is eligible for enrollment, if testing is not available. If a symptomatic person tests negative for SAR-CoV-2, they are <u>not</u> eligible for enrollment.

Mean Incubation period is ~5.2 days, thus we wish to limit enrollment to those with a higher risk of progression and deliver study medicine in a time period to intervene to

prevent disease or ameliorate disease (i.e. start of study medicine by <=4 days after exposure). The current (as of March 17, 2020) delays in testing makes this window particularly tight, and it may need to be relaxed in the future via protocol amendment.

In clinical practice of tropical medicine, chloroquine or hydroxychloroquine are prescribed without any baseline laboratory testing or monitoring.

Chronic use of hydroxychloroquine for >1 year can cause retinopathy or cardiomyopathy, thus persons with baseline conditions will be excluded. Study medicine is excreted via the kidney with dose reduction recommended in CrCl <30 cc/min (Stage 4 Kidney Disease). G-6-PD deficiency is listed as a caution on the FDA label. G-6-PD testing is not routinely performed in clinical care prior to giving hydroxychloroquine prescriptions (unlike with primaquine). Medication exclusions are for possible drug-drug interactions, particularly with cardiac arrhythmia medicines with a caution on the FDA-package insert.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Participants will be randomized via permuted block randomization. Randomization will be recorded on an electronic log by the pharmacy. Study investigators and subjects will be blinded. Randomization will be stratified by symptom/disease status at time of entry.

5.3.2 Masking Procedures

Participants will be provided masked study medicine, shipped by courier (e.g. FedEx). The intervention vs. placebo will not be identical; however, participants and outcome assessors will be masked to their assignment.

5.3.3 Reasons for Withdrawal

Participants may withdraw at any time point at their discretion.

5.3.4 Handling of Withdrawals

Withdraws will be counted as failures for the secondary endpoint of completion of study medication.

5.3.5 Termination of Study

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Unexpected, significant, or unacceptable risk to subjects
- Interim analyses by the DSMB.
- Insufficient compliance with protocol requirements
- Data are not sufficiently complete and/or not evaluable
- Regulatory authorities decide that study should be terminated

If the study is prematurely terminated for harm, current subjects will complete follow up, and no further subjects will be enrolled. If the study is terminated due to benefit, then the study will immediately convert into an open-label prospective cohort to collect further observational data on the safety and efficacy of the intervention, up to the IRB approved recruitment limit.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

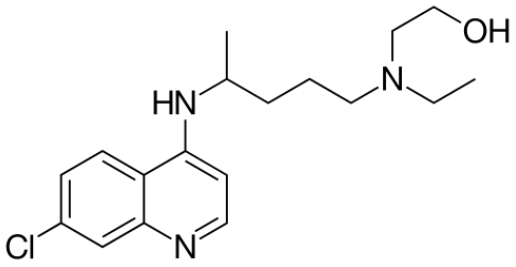
FDA-approved formulation of hydroxychloroquine will be purchased.

6.1.2 Formulation, Packaging, and Labeling

The study medicines will be packaged by the MHealth Investigational Drug Services. Dispensed medications will be delivered by courier (e.g. Fedex) to study participants.

6.1.3 Drug Description:

Hydroxychloroquine sulfate



6.1.4 Formulation: 200mg tablet (= 155 mg base of chloroquine)

6.1.5 Pharmacokinetics:

- Absorption: Rapid and almost completely
- Distribution: Widely distributed into body tissues
- Metabolism: Partially hepatic to main metabolyte of desethylchloroquine
- Excretion: Urine (>=50% as unchanged drug); acidification of urine increases elimination
- C_{max} = 1.2 nmol/mL = 1.2 μmol/L = 1.2 μM at 400mg single dose.[5,7]
- T_{max} = 2.4 hours
- $T_{1/2}$ = 172 ± 39 hours = 7.1 +1.6 days
- AUC_{last} = 75.4 ± 47 nmol/h/mL
- This C_{max} is in the therapeutic window for SARS-COV2 activity.
- Steady state doses for 400mg dose is 974 μg/L = 2.24 μM [8], thus a 600mg dose should generate approximately 3.4 μM , which is above the EC50 of viral inhibition of 1.3 μM (EC50 = 50% inhibition; however, the more inhibition the better, likely).

Population PK parameter modeling: 5 day regimen

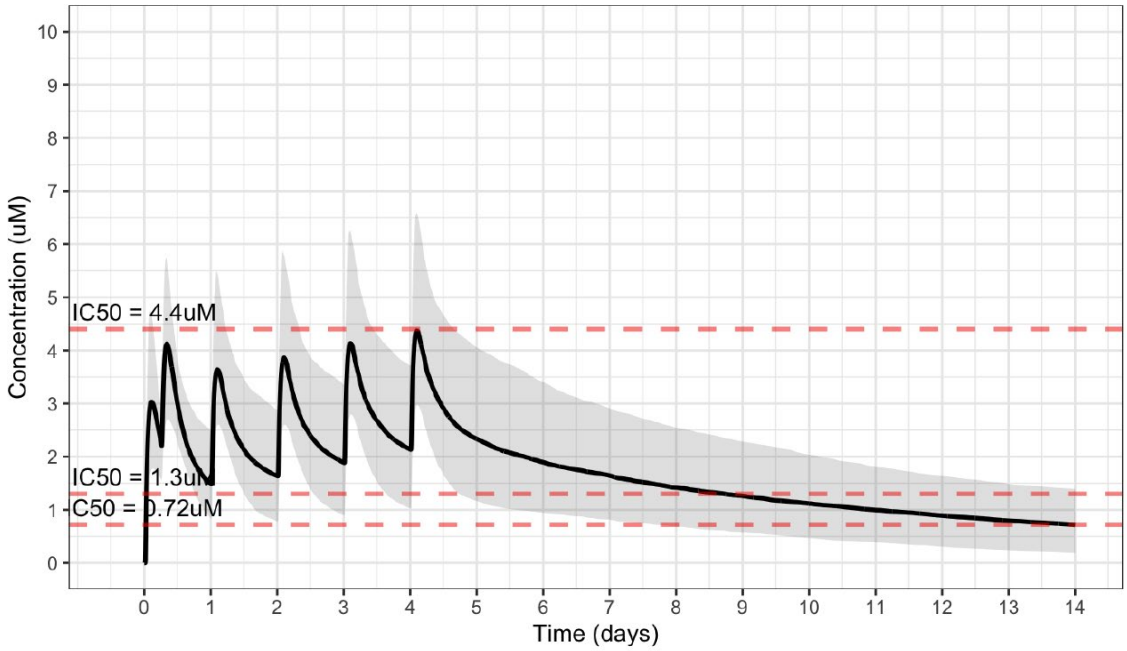
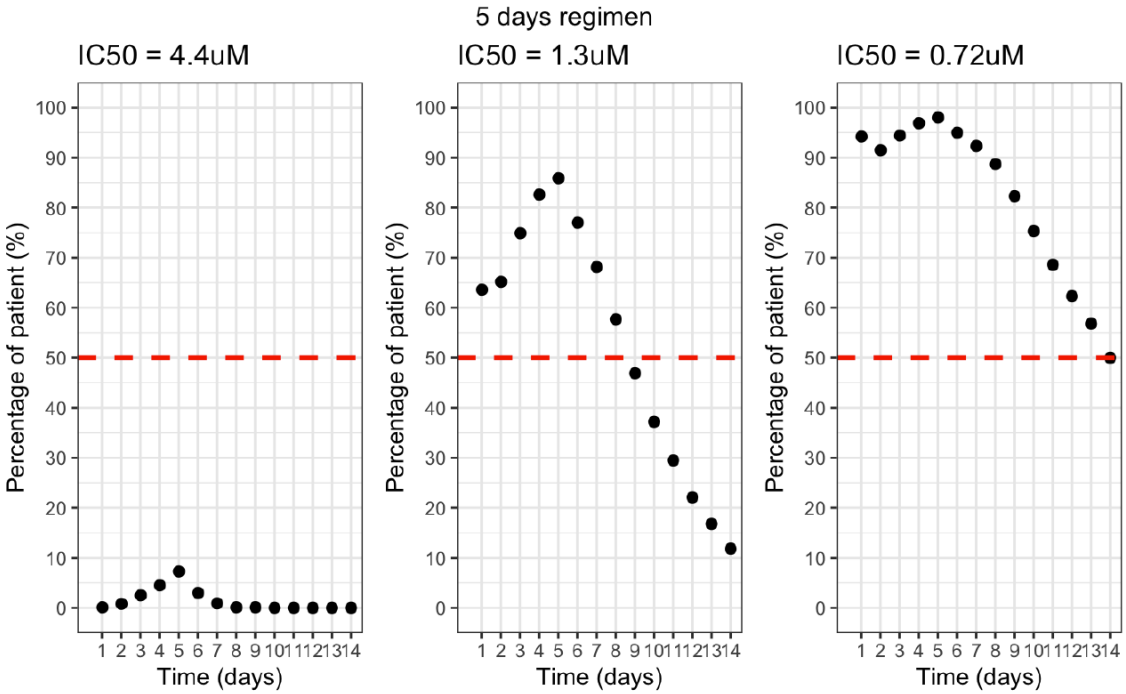


Figure courtesy of Dr. Mahmoud Al-Kofahi of College of Pharmacy, Univ. of Minnesota

The EC50 has been reported as 0.72 μM [5], although this is not a precise measurement, and should be view with a range of error present (but not reported). The EC50 is the point of 50% maximal inhibition, so more drug would be better (balanced against toxicity and drug supply). The percentage of persons achieving a 24 hour level above the EC50 is as follows (**Figure**).



6.1.6 Product Storage and Stability

Store at room up to 30° C (86° F). Dispense in a tight, light-resistant container.

6.2 Dosage, Preparation, and Administration of Investigational Product

6.2.1 Drug/Device Handling: Hydroxychloroquine or placebo will be dispensed by the MHealth Investigational Drug Service (IDS) Pharmacy. To do so, study investigator will send a prescription to the IDS Pharmacy, the pharmacy will randomize the subject, and dispense the appropriate study medicine. The medicine will then be provided to research volunteers via FedEx / courier delivery in the United States.

6.3 Modification of Investigational Product for a Participant

With mild side effects, participants will be instructed to split the 3 tablet daily dosing into multiple times per day.

In the event of substantial side effects, participants may discontinue the study medication.

In the event of the development of acute kidney injury with creatinine clearance <30 mL/min, the dose should be reduced by one-third.

6.4 Accountability Procedures for the Investigational Product:

Accountability will be via self-report at the day 5 virtual visit.

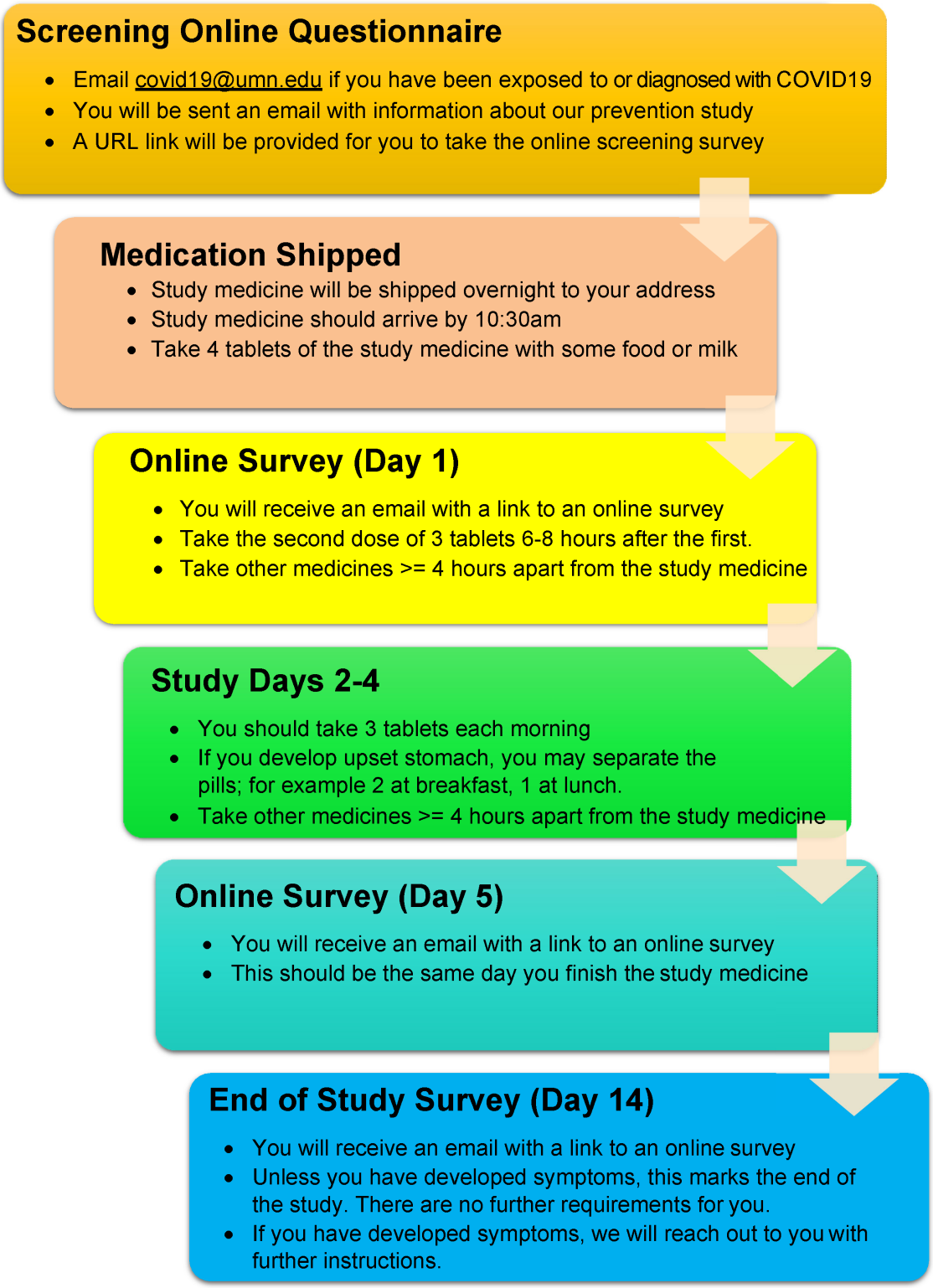
6.5 Assessment of Subject Compliance

Adherence will be via self-report at day 5 virtual visit.

6.6 Concomitant Medications/Treatments

Participants may receive other concomitant medications or therapies, and will be asked to report these in regards to other therapies received in the event of hospitalization.

7 STUDY SCHEDULE



7.1 Screening

- Baseline screening for eligibility
- Informed consent by self-administered
- This will be performed via a web-based form. Eligibility criteria will be by self-report.

7.2 Enrollment/Baseline

Randomization (Day 0)

- Participants will be randomized by a computer-generated algorithm using a permuted block randomization sequence.
- Randomization will be stratified by symptomatic vs. asymptomatic status at baseline.
- Investigational pharmacy will dispense the masked study medicine
- Study personnel will then FedEx study medicine to the participant
- Participant will be sent an email to expect medication to arrive by 10:30am

7.3 Follow-up

- Day 1 Visit
    - Participant will confirm receipt of study medication

- Day 5 Visit
    - Participant clinical status check-in
    - Assess adherence to intervention

7.4 Final Study Visit

- Day 14 Visit
    - Participant clinical status check-in
    - Assess adherence to intervention

7.5 Early Termination Visit

If participants develop new / worsening symptoms of coronavirus, they will be directed to their healthcare provider and/or local public health authority. Follow up of hospitalized patients up to 90 days for their final outcome.

7.6 Unscheduled Visit

Subjects will be provided a central email contact: faq.covid19@gmail.com as a contact point for questions or concerns. This email will forward to an on-call study physician who will call the participant to resolve their concerns.

Additionally, email communications will contain a URL for a sick visit web-form that participants can note their current development of symptoms of medication side effects. This will be the same follow up eCRF sent on Day 1, 5, and 14. This can be completed multiple times.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Clinical evaluations will be by self report

8.2 Laboratory Evaluations

There are no laboratory evaluations in the protocol.

Clinical outcomes are by self-report.

SARS-COV2 positivity is by self-report.

Informed consent will request permission to contact local public health authorities or their medical provider in the event of lost to follow up or COVID19 disease.

There is no incentive to be dishonest, and we believe healthcare workers in particular will take their responsibilities seriously.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Hydroxychloroquine has a track record of safety since its FDA-approval in 1955. As an already, FDA-approved medicine, this trial is designed as a pragmatic trial in the setting of a public health emergency.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Hydroxychloroquine has an excellent safety track record, being first FDA-approved in 1955. Adverse events will not be captured, unless they result in hospitalization. See Serious Adverse Events below.

Expected adverse events would include normal events within the general population as well COVID19-related disease events which may include need for hospitalization, pneumonia, respiratory failure, sepsis, and death.

9.2.2 Reactogenicity (for Vaccine Studies and Some Therapeutic Trials)

Not applicable

9.2.3 Serious Adverse Events

Hospitalization or death are protocol-defined endpoints.

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Not applicable

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if it results in any of the following outcomes:

- Death,
- a life-threatening adverse event (as below),

- hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
    Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening adverse event. An AE is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. For life threatening AEs, subjects would be recommended /expected to be hospitalized.

Based on the known safety track record of hydroxychloroquine, this pragmatic protocol will focus on death, life-threatening AEs, and hospitalizations. Incapacity / permanent disability is a possibility with COVID19, but this is not associated with hydroxychloroquine. In the event of incapacity, the subject would be expected to be hospitalized.

Hydroxychloroquine and chloroquine are not known to cause teratogenic events and are viewed as safe in pregnancy, especially with short term use. With this trial’s sample size, this will not further delineate this risk. COVID19 disease may indeed be teratogenic. For women who are pregnant, we will ask to follow them through the end of their pregnancy.

Thus the hospitalization or death secondary endpoint will capture relevant SAEs.

9.3.2 Regulatory Reporting

As hydroxychloroquine is an FDA-approved medicine being used at standard dosing, reporting to regulatory authorities will occur in summary format after each DSMB reports and at a frequency of at least annually.

Serious unexpected suspected adverse reactions (SUSARs) which are not expected with COVID19 nor listed in the FDA package insert will be reported to the IRB. Those SUSARS which are deemed by an independent medical monitor to be related to the study medicine will be reported to the FDA and IRB.

9.3.3 Reporting of Pregnancy

Chloroquine and hydroxychloroquine are not known to be teratogenic. Chloroquine and hydroxychloroquine can accumulate in neonatal eyes. Conversely, the risk of severe COVID19 infection is unknown, but likely is a heightened risk in pregnant women. The CDC states, “We do not have information on adverse pregnancy outcomes in pregnant women with COVID-19. Pregnancy loss, including miscarriage and stillbirth, has been observed in cases of infection with other related coronaviruses (SARS-CoV and MERS-CoV) during pregnancy. High fevers during the first trimester of pregnancy can increase the risk of certain birth defects.”

Thus, the risk/benefit would favor the enrollment of women who may be or are pregnant, so as to not discriminate against pregnant women.

For women who are pregnant, we will ask to have follow through the end of their pregnancy to assess outcome of the pregnancy via a brief survey.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Participants who are hospitalized for COVID19 or SAEs will have up to 90 day follow up conducted to assess their final outcome. Management will be as per the participant’s local healthcare provider.

9.5 Safety Oversight (DSMB)

A data and safety monitoring board (DSMB) will oversee the trial. The quorum will include three members and a biostatistician. The PI will be a non-voting observer, providing input as requested.

9.6 Halting Rules

A Lan-DeMets spending function analog of the O’Brien-Fleming boundaries will be provided at each DSMB report for the disease severity outcome, thus dependent on precise DMSB time period, the difference necessary to trigger early stoppage will vary, converging toward >35% relative risk reduction by study conclusion. The provided table assumes four interim analyses with the final analysis with an overall alpha=0.05.

Interim Analysis	Sample Size	| Z |	P-value
1	~375 (25%)	> 3.1	.001

2	~750 (50%)	> 2.6	.003
3	~1125 (75%)	> 2.02	.018
Final	1500 (100%)	> 1.72	.023

As the effect size is unknown, the O'Brien-Fleming boundaries are a conservative, yet being truncated at Z-score of 3.1 equating to a P-value of approx 0.001. At the first DSMB review, the stopping boundary is unlikely to be crossed. The purpose of this early review will assess the trends for safety/efficacy and allow for the DSMB to determine if more frequent reviews are appropriate. If more interim analyses are desired by the DMSB, the Lan-DeMets spending function will be recalculated using O'Brien-Fleming boundaries and provided with each DSMB report.

Should a stopping boundary be crossed, we would recommend an analysis to determine whether the findings are consistent across secondary endpoints, such that a clear answer is achieved. **In the event of early halting due to efficacy, the study will immediately convert to an open label observational cohort of hydroxychloroquine prescribed to all consented participants.**

Based on the public health situation, the DSMB has the prerogative to alter the stopping rules.

Sample Size Re-estimation:

At time of the second DSMB review, a sample size re-estimation should occur based on the disease transmission rate in the control group. The apriori assumption (based on limited data) is 10% transmission risk. The effect size to be powered will remain a 50% relative reduction, and any re-estimation will not account for accumulating data in the intervention arm. For example, if the incidence of COVID-19 disease in the control arm is only 5%, then the sample size will increase four-fold to 3000 participants per arm.

Futility Analysis:

If the conditional power is <20% at the time of the second interim analysis with approximately 50% of participants enrolled, discontinuation should be considered as a possible recommendation by the DSMB. The sample size re-estimation will be considered here as well as the pace of enrollment.

10 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected and that the reported trial data are accurate, complete, and verifiable. Clinical monitoring also ensures that conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and Sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions. Monitoring will be the responsibility of the University of Minnesota.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

Hydroxychloroquine is superior to placebo for preventing progression to COVID19 disease.

Hydroxychloroquine is superior to placebo for preventing progression among those with symptomatic mild COVID19 disease preventing hospitalization/death.

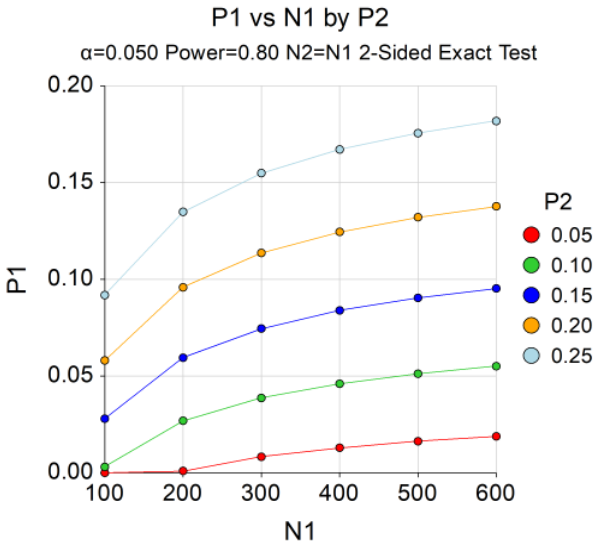
11.2 Sample Size Considerations

Two strata of 1500 subjects each: 1) Asymptomatic exposures; 2) symptomatic COVID-19 disease

The planned sample size is up to 750 participants per arm, based on the assumptions of:

- Transmission from COVID19 case to close contacts is ~10% with placebo.
- Progression from symptomatic illness to hospitalization is ~10% with placebo (conservative estimate on rate of progression, based on probable enrollment of younger/healthier, more internet savvy population enrolling)
- The primary analysis will be intention to treat.
- Type 1 error is 0.05 (2-sided) and power = 0.90.
- N=621 per arm for 90% Power to detect a 50% relative risk reduction for both disease incidence as well as the ordinal scale of disease severity .
- With up to 20% dropout, N=750 per arm

As the transmission frequency increases, the sample size dramatically decreases, need to demonstrate an effect (**Figure Right**). For instance at 20% control prevalence of transmission (orange line), a sample size of n=200 per arm would have 80% power to detect a ~52%reduction to 9.6% transmission in the intervention arm. Conversely, if transmission frequency is 5%, then there is 80% power to detect an effect size of ≥67% reduction in transmission (to 1.63%).



11.3 Planned Interim Analyses (if applicable)

Interim analyses will focus on the statistical testing of the primary endpoint with descriptive reporting of the secondary endpoints as well. Interim analyses will be conducted after enrollment of approximately: 25%, 50%, 75%, and 100% of participants are enrolled. This interval may be modified by the DSMB.

Interim analyses will assess also for:

a) Evidence of harm or unintended consequences
b) Appropriateness of baseline assumptions, specifically the incidence of disease in the control group;
c) Futility, particularly from time of the third DSMB onwards.

11.4 Final Analysis Plan

Those with symptomatic disease at baseline will be separately analyzed. Analysis will be stratified by baseline strata of 1) asymptomatic exposure; 2) symptomatic COVID-19 disease.

Asymptomatic Cohort

Incidence of new COVID19 disease will be assessed via Fisher's Exact test, among those who are asymptomatic at baseline.

- The primary analysis will use PCR+ confirmed disease.
- However, if the absence of sufficient testing supplies continues, outpatients will not be offered SARS-CoV-2 testing unless they are sick enough to be hospitalized. Thus, an alternative a priori planned analysis will define incident COVID19 disease as a composite of SARS-CoV-2 PCR+ confirmed COVID-19 disease OR symptomatic disease (i.e. possible) COVID-19 in those without testing.

Symptomatic Cohort

The primary endpoint for those who are symptomatic at entry will be assessed on an ordinal scale to estimate a proportional odds model. The primary hypothesis test will be based on whether the commons Odds Ratio for prophylaxis is equal to one.

- For those with symptomatic illness at baseline, a three score ordinal scale will also be used of: i) illness without hospitalization; ii) hospitalization/post-hospital discharge; iii) Hospitalization with ICU stay/death). Outcomes will be assessed at Day 14. A sensitivity analysis will also be performed at Day 56 to capture delayed hospital outcomes.

- Further descriptive analysis will further report hospitalization, hospitalization with ICU, respiratory failure requiring mechanical ventilation, and/or death; however, these subgroups are expected to be small and will not be formally statistically tested.

Analysis will be by modified, intention to treat limited to participants who receive at least one dose of the study medicine. Participants who become symptomatic with COVID19 before receiving the study medicine will be censored from the primary analysis on incident disease, but will be separately described.

Secondary endpoints will be assessed via Fisher's Exact test for the proportions by study arm.

Among those with symptoms, severity of symptoms (recorded on a 0-10 visual analog scale) will be compared via Mann-Whitney U by study arm at day 5 and 14.

Duration of PCR-positivity with the time to PCR negative will be assessed between trial arms by a cumulative incidence function.

Duration of hospitalization will be assessed via independent *t*-test.

A priori subgroup analyses will include assessment by:

- Confirmed SARS-CoV-2 disease or disease exposure

- Healthcare worker vs. Household contact
- Days from Exposure
- Decile of age
- Sex as a biological variable
- Censored subjects, who became symptomatic before receipt of the first dose of study medicine on D#1, will be separately analyzed and reported.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source documents will include internet forms self-completed by participants directly entered into a RedCAP database.

This protocol is based on self-report.

This internet-based protocol is meant to enable a large number of participants to be recruited, quickly as well as maintain the safety of the research staff. In person visits, create a public health

Participants will be asked to provide consent to obtain medical records from their healthcare provider or public health official, if there is the need to verify outcomes – for SARS-CoV-2 test results or hospitalizations.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Study medications will be FDA-approved following Good Manufacturing Practice.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization guidelines), Declaration of Helsinki, and International Ethical Guidelines for Biomedical Research Involving Human Subjects, applicable U.S. government regulations and institutional research policies and procedures. All investigators must have received human subject protection and GCP training prior to human subject involvement.

14.2 Institutional Review Board

Prior to the initiation of the study, the protocol, all informed consent forms and the participant Information materials will be submitted to and approved by the single IRB of record. Likewise, any future amendments to the study protocol will be submitted and approved by the IRB before implementation. This protocol and any amendments will undergo review and approval by the Human Subjects Board at the University of Minnesota under DHHS Assurance FWA00000312.

14.3 Informed Consent Process

- Written informed consent will be obtained via an English-language, internet-based web form. If potential participants have questions, they may contact faq.covid19@gmail.com to reach a study staff member to answer their questions about research, either via email or a phone call.
- After completion of reading the form, participants will be assessed for comprehension, querying:
    - Concept of Randomization to hydroxychloroquine or vitamin placebo
    - Whether hydroxychloroquine is known to be effective in preventing disease

- Duration of the study? (14 days)
- Duration of taking the study medicine (5 days)
- When follow up surveys will be sent (Days 1, 5, and 14)
- If hydroxychloroquine can be shared? (No)

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

- Persons under 18 years of age are not eligible to participate. COVID19 has 0% mortality in children, and rate of progression to symptomatic disease may likely be different. Furthermore, pediatric dosing is weight based, making remote administration more complicated.

14.4 Exclusion of Women, Minorities, and Children

- Persons under 18 years of age are not eligible to participate. COVID19 has 0% mortality in children and young adults.
- Non-English speaking adults are not eligible as the webpage and consents will only be available in English.

14.5 Subject Confidentiality

- Interaction will be via internet-based RedCAP ECRFs conforming to required U.S. privacy and server security standards.
- Clinical data will be entered into a study specific database by designated staff on a regular basis from completed electronic Case Record Forms (eCRF). Access to database will be given to authorized personnel only (members of the immediate study team). eCRF and trial documents will be kept in a secure database.
- Documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the participant except as necessary for monitoring by the IRB or public health authorities
- No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.

14.6 Future Use of Stored Specimens

- No specimens are to be collected.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Investigators will maintain a REDCAP database of study records.

Survey forms will be self-completed by study participants.

15.2 Data Capture Methods

- Data will be obtained via internet-based REDCAP forms.

15.3 Types of Data

- Participants will be asked to provide data regarding COVID19 exposure timing and location. They will also be asked to provide ongoing symptom reports during the follow-up period.

15.4 Timing/Reports

- An enrollment progress report will be generated monthly
    - Participants Enrolled
    - Participants on study
    - Participants completed the study
    - Lost to Follow Up
    - Cumulative COVID19 (pooled, both arms)
    - Cumulative Hospitalizations (pooled, both arms)
- A data safety monitoring board (DSMB) will review data after every 100 participants complete 14 days of follow-up.
- De-identified data will be shared with the research team members for analysis.

15.5 Study Records Retention

- No paper documents will be retained or stored.
- Digital records will be kept in a secure server setting.

15.6 Protocol Deviations

Protocol violations will be reported to the IRB of record.

16 PUBLICATION POLICY

Publication will be expeditiously made with a full, de-identified data made available.

17 LITERATURE REFERENCES

1. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
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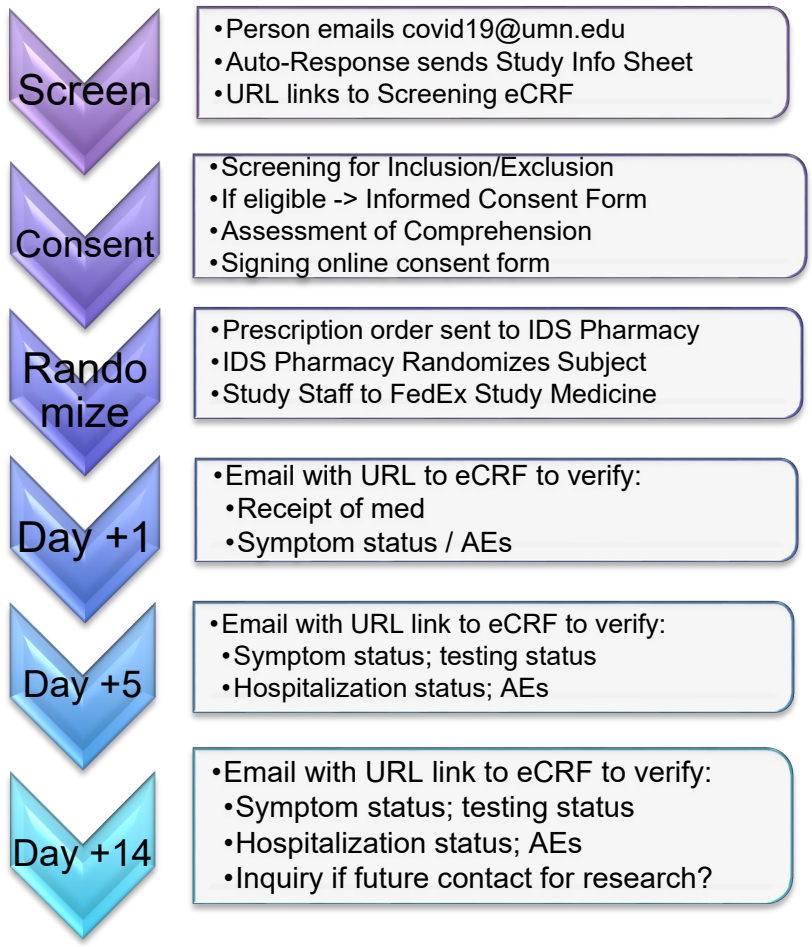
SUPPLEMENTS / APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Overview of Procedures



Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial

Short Title: COVID-19 PEP RCT

UMN IRB Number: STUDY00009267

FDA IND: 148257

ClinicalTrials.gov: NCT04308668

Principal Investigator: David R Boulware

Draft or Version Number: 2.3

24 April 2020

CONFIDENTIAL

STATEMENT OF COMPLIANCE

This protocol will utilize a single institutional review board (IRB) registered with the Office of Human Research Protections (OHRP) and issued a Federal Wide Assurance (FWA). The research will be reviewed and approved by the IRB and will be subject to continuing review [45 CFR 46.103(b)].

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed:  Date: 4/24/2020

Name
Title

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience	
CFR	Code of Federal Regulations	
CONSORT	Consolidated Standards of Reporting Trials	
CFR	Code of Federal Regulations	
COVID19	coronavirus disease 2019	
SRS-CoV	SARS coronavirus	(i.e. circa 2003)
SARS-CoV-2	SARS coronavirus 2	(i.e. circa 2019)
CRF	Case Report Form	
CRO	Contract Research Organization	
DCC	Data Coordinating Center	
DHHS	Department of Health and Human Services	
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH	
DSMB	Data and Safety Monitoring Board	
eCRF	Electronic Case Report Form	
FDA	Food and Drug Administration	
FWA	Federalwide Assurance	
GCP	Good Clinical Practice	
HIPAA	Health Insurance Portability and Accountability Act	
ICF	Informed Consent Form	
ICH	International Conference on Harmonisation	
IDS	Investigational Drug Services	
IEC	Independent or Institutional Ethics Committee	
IND	Investigational New Drug Application	
IRB	Institutional Review Board	
MERS-CoV	Middle East respiratory syndrome coronavirus	
MOP	Manual of Procedures	
N	Number (typically refers to subjects)	
NIAID	National Institute of Allergy and Infectious Diseases, NIH	
NIH	National Institutes of Health	
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS	
OHRP	Office for Human Research Protections	
OHSR	Office for Human Subjects Research	
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS	
PCR	Polymerase chain reaction	
PHI	Protected Health Information	
PI	Principal Investigator	
SAE	Serious Adverse Event	
SOP	Standard Operating Procedure	
US	United States	
WHO	World Health Organization	

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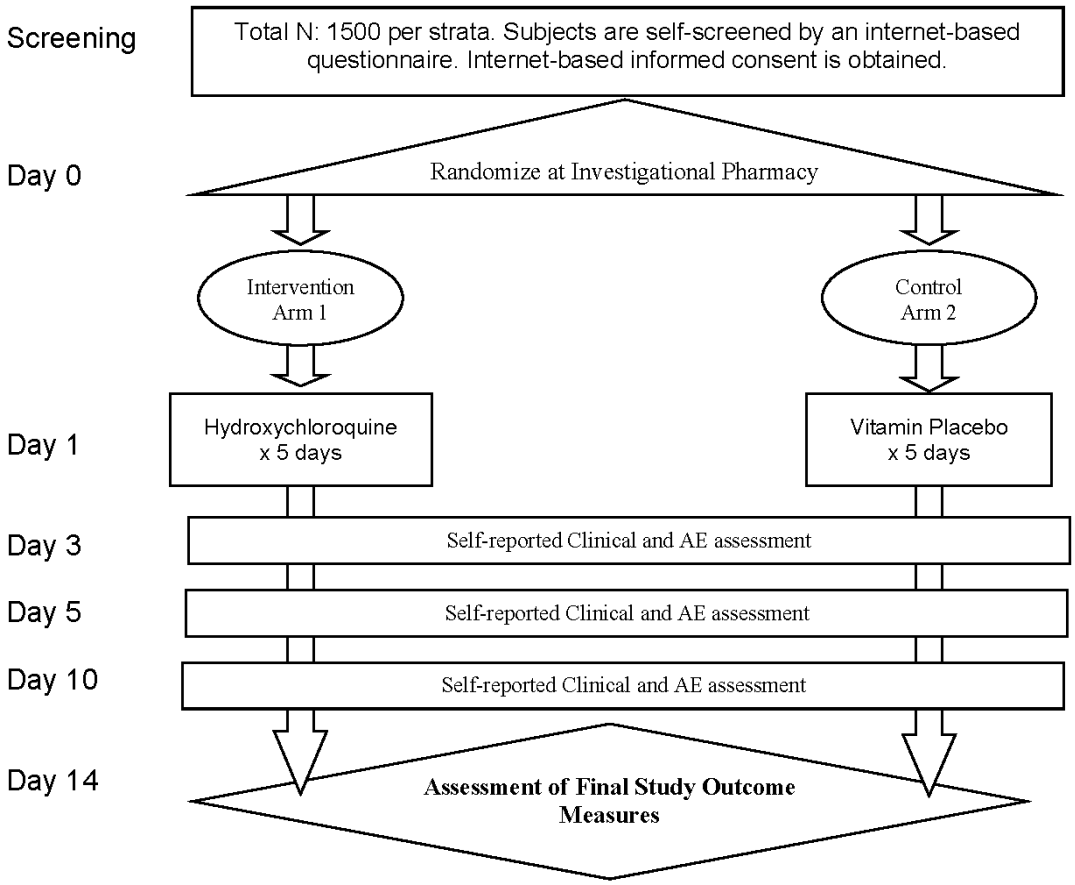
Summary

Full Title:	Post-exposure prophylaxis or Preemptive Therapy for coronavirus: A Pragmatic Randomized Clinical Trial
Short Title:	COVID-19 PEP RCT
Clinical Phase:	III
Sponsor:	Investigator-Initiated Protocol, University of Minnesota
Principal Investigator:	David R Boulware, MD MPH
Accrual Ceiling	3000
Study Population	• Adult Household contacts or Healthcare workers exposed to persons with COVID-19 disease within 4 days (n=1500), or • Non-hospitalized adults with symptomatic COVID-19 disease within 4 days of onset (n=1500)
Objective	1) Test if hydroxychloroquine can prevent development of COVID-19 disease after known exposure to the SARS-CoV2 virus. 2) Test if early preemptive therapy in non-hospitalized adults with symptomatic COVID-19 disease can prevent disease progression and hospitalization
Study Design	Double-blind, randomized placebo-controlled clinical trial Internet-based trial driven by self-report. Study medicine delivered by FedEx to consented participants. Follow up through 14 days, with SAEs followed up to 90 days
Intervention Arm:	Hydroxychloroquine 200mg tablet.

	800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600 mg once a day for 4 consecutive days (5 days in total) *(This is a modified malaria dosing for hydroxychloroquine)*
Control Arm:	Placebo 4 tabs once, followed in 6 to 8 hours by 3 tabs, then 3 tabs once a day for 4 consecutive days (5 days in total)
Primary Endpoint in Asymptomatic Cohort	● Incidence of COVID-19 disease within 14 days among those who are asymptomatic with known exposure
Primary Endpoint in Symptomatic Cohort	● Change in symptom severity score (visual analog scale 0-10) over 14 days
Secondary Endpoints	1. Incidence of Hospitalization for COVID-19 or death 2. Incidence of confirmed SARS-CoV-2 detection 3. Incidence of possible COVID-19 symptoms 4. Incidence of all-cause study medicine discontinuation 5. Severity of symptoms at Day 5 and 14 by visual analog scale 6. Ordinal Scale of COVID-19 disease maximum severity at day 14 among those who are symptomatic at trial entry
Duration of Participation	Recruitment and follow up will be internet-based. ● 14 days of active participation ● Up to 90 days follow up for those with COVID-19 diagnosis to assess final outcome or dried blood spot collection for antibody serologies.
Inclusion Criteria	● Exposure to COVID-19 within 4 days, either as: ○ Occupational exposure, or ○ Household contact. OR ● Individual with symptomatic COVID-19 disease confirmed by PCR+ or by compatible symptoms with exposure to known PCR+ case with <=4 days of symptoms. ● Age >=18 years of age ● Provision of Informed Consent
Exclusion Criteria	• Current hospitalization • Allergy to chloroquine or hydroxychloroquine • Prior retinal eye disease • Concurrent malignancy requiring chemotherapy • Known Chronic Kidney disease, Stage 4 or 5 or dialysis.

	• Known glucose-6 phosphate dehydrogenase (G6PD) deficiency. • Known Porphyria • Weight <50 kg • Structural or ischemic heart disease • Personal or family history of QT prolongation • Current use of: hydroxychloroquine, chloroquine, mefloquine, or cardiac medicines of: amiodarone, digoxin, dofetilide, flecainide, procainamide, propafenone, or sotalol • Current use of QT prolonging medicines, including azithromycin (Refer to protocol for full list).
Stratification	Randomization will be stratified by baseline status of COVID-19 disease vs. asymptomatic with exposure. Analyses will be separate for asymptomatic vs. symptomatic cohorts
Statistical Assumptions	● 10% attack rate for close contracts (or 10% progression of disease to hospitalization among those symptomatic at entry) ● Comparison of Proportions by Fisher's Exact test for disease incidence; ● Comparison of ordinal scale of disease severity by proportional odds model ● N=621 sample per arm has 90% power to detect a 50% relative risk reduction (i.e. $\leq$5.0%) in disease incidence or 50% decrease in the ordinal disease severity (to $\leq$4.25% disease incidence and $\leq$1% hospitalization). ● 20% dropouts, inflates sample size to n=750 per arm

Schematic of Study Design:



If hospitalization occurs, this SAE will be followed for up to 90 days

For participants who develop symptomatic disease, they will be followed for up to 90 days to assess final outcome status in the event of hospitalization.

Stratification is based on symptom status at baseline

1. 1500 asymptomatic healthcare workers or household contacts exposed to COVID-19
2. 1500 symptomatic COVID-19 outpatients

1 KEY ROLES

Individuals:

Principal Investigator: David R. Boulware MD, MPH, CTropMed

Co-Investigator: Sarah Lofgren, MD

Co-Investigator: Alison Galdys, MD

Co-Investigator: Matthew Pullen, MD

Co-Investigator: Radha Rajasingham, MD

Co-Investigator: Caleb Skipper, MD

Medical Monitor: Mahsa Abassi, DO MPH

Pharmacologist: Melanie Nicol, PharmD, PhD

Biostatistician: Kathy H Hullsiek, PhD

Associate Statistician: Ananta Bangdiwala, MS

Associate Statistician: Nicole Engen, MS

Institution: Division of Infectious Diseases, Department of Medicine, University of Minnesota, Minneapolis, MN

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Significance of Research Question/Purpose:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rapidly emerging viral infection causing COVID19. The current strategy uses a public health model of identifying infected cases, isolation, and quarantine to stop transmission. Once exposed, observation is standard-of-care.

No effective therapy currently exists for treatment. The lack of effective therapy diminishes persons presenting post-exposure for self-quarantine. Having an effective post-exposure prophylaxis, even if only partially effective, may additionally create synergy for the public health strategy of case identification and isolation – if a safe prophylaxis is available.

People who develop COVID-19 disease generally develop signs and symptoms, including mild respiratory symptoms and fever, after an average of 5-6 days after exposure (i.e. mean incubation period). The range of the incubation period is between 1 to 14 days.[1]

Most people infected with the COVID-19 virus have mild disease and recover. Approximately 80% of laboratory-confirmed patients have had mild to moderate disease, which includes non-pneumonia and pneumonia cases, 14% have severe disease, and 6% are critically ill with respiratory failure, shock, and/or multiple organ dysfunction [1].

Preliminary Data:

Chloroquine has *in vitro* activity in cell lines against SARS-CoV and SARS-CoV2. In a Vero E6 cell line, the half-maximal effective concentration (EC50) activity of chloroquine was 1.13 μM against SARS-CoV2 [2]. Hydroxychloroquine is functionally equivalent as chloroquine.

Another compound under treatment trials, remdesivir (Gilead) had an EC50 of 0.77 μM [2]. Remdesivir (Gilead) is not FDA-approved and in limited quantities. Hydroxychloroquine is FDA-approved and globally is inexpensive. Chloroquine is no longer broadly available in the USA.

Existing Literature:

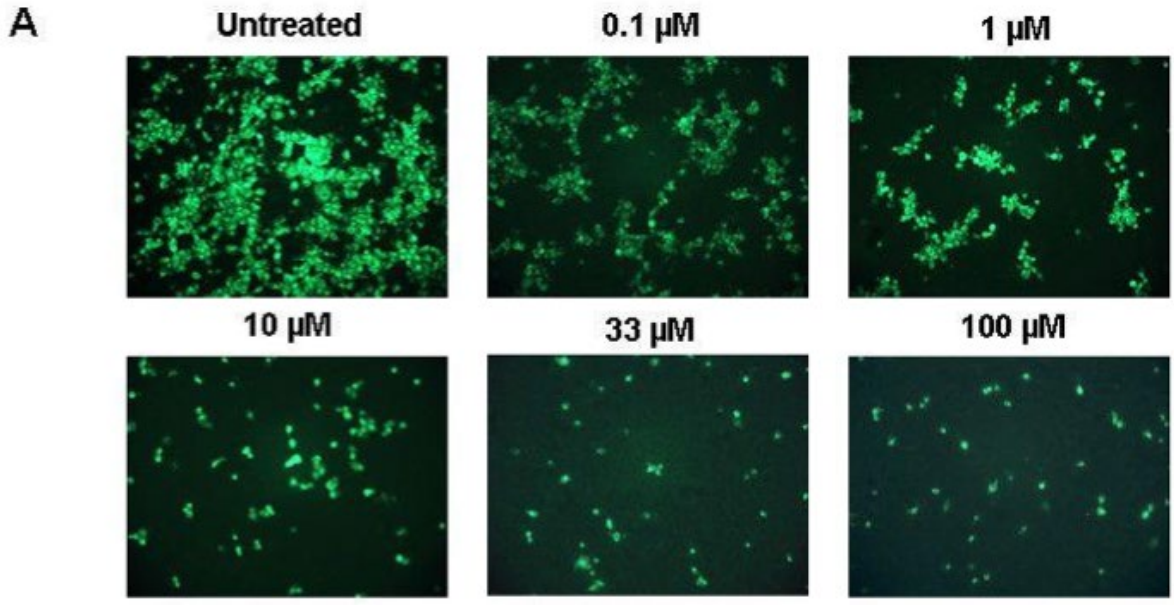
Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy is poorly understood as a gold standard randomized clinical trial has not been conducted.

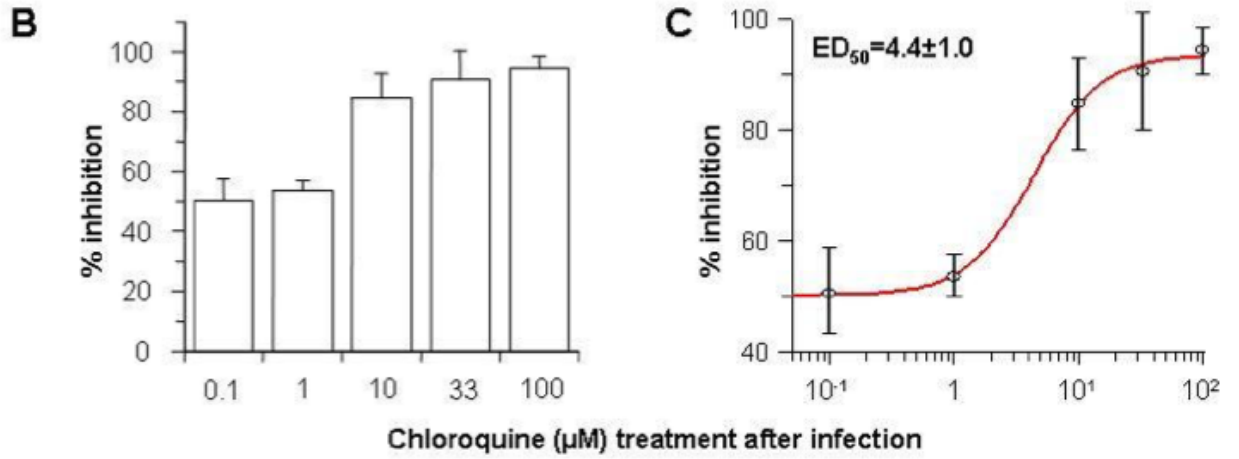
After the original 2003 SARS outbreak, screening of compounds was performed. The Special Pathogens Branch of the Division of Viral and Rickettsial Diseases at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia investigated chloroquine.

CDC investigators reported that post-infection chloroquine treatment was effective in vitro at preventing the spread of SARS-CoV infection in an in vitro cell-based system [3]. Vincent et al reported:

> "In order to investigate the antiviral properties of chloroquine on SARS-CoV after the initiation of infection, Vero E6 cells were infected with the virus and fresh medium supplemented with various concentrations of chloroquine was added immediately after virus adsorption. Infected cells were incubated for an additional 16–18 h, after which the presence of virus antigens was analyzed by indirect immunofluorescence analysis. When chloroquine was added after the initiation of infection, there was a dramatic dose-dependent decrease in the number of virus antigen-positive cells (**Fig. 2A**). As little as 0.1–1 μM chloroquine reduced the infection by 50% and up to 90–94% inhibition was observed with 33–100 μM concentrations (**Fig. 2B**). At concentrations of chloroquine in excess of 1 μM, only a small number of individual cells were initially infected, and the spread of the infection to adjacent cells was all but eliminated. A half-maximal inhibitory effect (EC50) was estimated to occur at 4.4 ± 1.0 μM chloroquine (**Fig. 2C**). These data clearly show that the addition of chloroquine can effectively reduce the establishment of infection and spread of SARS-CoV if the drug is added immediately following virus adsorption." [3]

Figure 2. Post-infection chloroquine treatment reduces SARS-CoV.





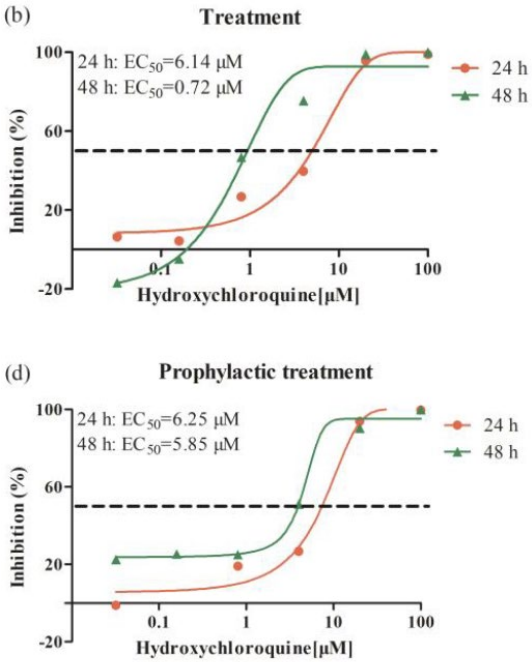
Vincent et al also reported: “Since we observed antiviral effects by chloroquine immediately after virus adsorption, we further extended the analysis by adding chloroquine 3 and 5 h after virus adsorption and examined for the presence of virus antigens after 20 h. We found that chloroquine was still significantly effective even when added 5 h after infection (Fig. 3); however, to obtain equivalent antiviral effect, a higher concentration of chloroquine was required if the drug was added 3 or 5 h after adsorption.” [3]

Further experiments demonstrated that chloroquine impaired the terminal glycosylation of angiotensin-converting enzyme-2 (ACE2) receptor, which is the binding site for the envelope spike glycoprotein of SARS-CoV and SAR-CoV2 [3].

Conversely, chloroquine did <u>not</u> have activity against Middle East respiratory syndrome coronavirus (MERS-CoV), which may be related to MERS binding to CD26 receptor protein [4].

In a March 9, 2020 publication, hydroxychloroquine was found to have greater activity than chloroquine [5]. **The SARS-CoV-2 EC 50 values for hydroxychloroquine were 6.14 μM at 24 hours and 0.72 μM at 48 hours,** [5]. Conversely, chloroquine EC50 values were >100 μM at 24 hours and 18.01 μM at 48 hours [5]. This inhibition assay was performed with Vero cells using an infectious dose of 100 plaque forming units.

Figure 3 displays the antiviral activities of hydroxychloroquine for treatment or prophylaxis against SARS-CoV-2 *in vitro* [5].



Existing Clinical Data

There is accumulating clinical data on treatment of hospitalized patients with COVID-19 infection with chloroquine or hydroxychloroquine. These data have been summarized by Pastick et al. as of April 15, 2020 [6]. To date, there is no conclusive evidence of clinical benefit of hydroxychloroquine for treatment of hospitalized patients.

There have been no studies of early therapy or preventative therapy.

Reference	Overall Findings	Limitations	Study design	Number of patients		Treatment regimen	Severity of illness (As reported)	Location	Outcomes
				HCQ	Control				
	Hydroxychloroquine (HCQ)								
Chen J, et al. [7]	No statistically significant differences in conversion rate by day 7 (86.7% vs. 93.3%, p>0.05). No difference in clinical outcomes between groups.	Full article only available in Chinese. Not peer-reviewed. Small sample size.	Randomized controlled trial	15	15	400mg HCQ for 5 days	Unknown severity; patients had symptoms for 6-7 days	Shanghai, China	At two weeks, all patients had negative viral nucleic acid tests.
Gautret et al. [8]	In unadjusted analyses, there were significantly reduced viral titers in the HCQ arm at day 6 (70% compared to 12.5% PCR negative, p<0.001). All six patients receiving HCQ and azithromycin were SARS-CoV-2 negative on day 6.	Study design. Small sample size/underpowered. Exclusion of six patients from analysis (no intention to treat analyses). Lack of long-term outcomes.	Non-randomized, non-blinded, open-label trial	26	16	600mg HCQ for 10 days	17% were asymptomatic 61% had upper respiratory symptoms 22% had chest CT confirmed pneumonia	Marseille, France	Six patients in the treatment arm were excluded from analysis (one died, three required ICU admission, one withdrew, one was lost-to-follow-up).

Chen Z, et al. [9]	Time to clinical recovery and cough remission were shortened in the HCQ group; resolution of pneumonia was higher in the HCQ group (80.6% vs. 54.8%) Two HCQ patients had mild adverse reactions (rash, headache).	Small sample size. Not peer-reviewed.	Randomized, parallel-group trial	31	31	400mg HCQ for 5 days	Mild illness (PaO2/FiO2 >300 mmHg) with chest CT confirmed pneumonia	Wuhan, China	Four patients in the control group developed severe illness (not defined).
Molina et al. [10]	8/10 had positive nasopharyngeal swabs at days 5-6 (80%, 95% CI: 49-94).	Small sample size. Not peer-reviewed.	Prospective open-label study	11	0	600mg HCQ for 10 days + azithromycin 500mg x1, then 250mg	10/11 were receiving supplemental O2	Paris, France	One patient died, two were transferred to the ICU, one had medications stopped secondary to QTc prolongation.
Gautret et al. [11]	Reduced nasopharyngeal viral titers at day 7 (83% negative) and 8 (93%). Mean length of hospitalization of 5 days.	Study design. Small sample size. Short follow-up time. Not peer-reviewed.	Non-randomized, non-blinded, open-label trial	80	0	600mg HCQ for 10 days + 500mg, followed by 250mg azithromycin	5% were asymptomatic 54% had pneumonia 92% of patients had a low national early warning score (NEWS) and mild disease	Marseille, France	Sixty-five (81.3%) patients survived to hospital discharge. Three patients required ICU admission and one died.
	Chloroquine (CQ)								
Gao J et al. [12]	CQ was stated to be superior to standard of care treatment in preventing exacerbation of pneumonia, reducing days to conversion rate, and shortening time to clinical recovery.	Combined patients from various ongoing studies. No statistical methodology.	Interim report	100	0	Not reported, likely varied from trial to trial.	NA	Qingdao, China	NA

2.2 Rationale

Current standard of care is observation and quarantine after exposure to COVID19.

As of March 6, 2020, the CDC estimates that the transmission of SARS-CoV2 after a U.S. household close contract is 10.5% (95%CI, 2.9 to 31.4%) [13]. Among all close contacts, the SARS-CoV2 transmission rate is estimated at 0.45% (95%CI, 0.12 to 1.6%) by the CDC. These estimates are based on monitoring of travel-associated COVID19 cases. Conversely, in a setting with community transmission, the secondary attack rate in China was 35% (95%CI, 27-44%) based on 48 transmissions among 137 persons in 9 index patients.

Chloroquine or Hydroxychloroquine may have antiviral effects against SARS-COV2 which may prevent COVID19 disease or early preemptive therapy may ameliorate disease severity. This trial will use a modification of standard malaria dosing of hydroxychloroquine to provide post-exposure prophylaxis / preemptive therapy.

Standard malaria treatment dosing is:

- 800mg once, then 400mg in 6-8 hours, then 400mg daily x 2 days (3 days in total).

We propose to dose for SARS-CoV-2 post-exposure prophylaxis at:

- 800mg once, then 600mg in 6-8 hours, then 600mg daily x 4 days (5 days in total).

The projected levels achieved will be approximately 4.4 μM which is at or above the half maximal effective concentration (EC50) where 50% viral inhibition would occur. A delayed start to prophylaxis will be occurring -- based on the intrinsic delay from the exposure to case notification to trial enrollment, and to receipt of the first medication dose. Thereby, higher doses may be necessary as seen in the CDC study [3]. Thus a malaria loading dose sequence will be used, but with higher daily doses thereafter to target reaching the above the EC50.

As the incubation period is 2-14 days with a mean incubation period of 5-6 days, we seek to deliver post-exposure prophylaxis by the morning of day 4 at the latest. (<=3 days is an inclusion criteria). We recognize this may turn “post-exposure prophylaxis” into more of a “preemptive therapy” for some subjects who rapidly develop disease after trial randomization. If hydroxychloroquine does not prevent disease for some, preemptive therapy may ameliorate the COVID19 disease severity. Attenuated disease may in turn be associated with reduced rates of transmission.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Short-term use of hydroxychloroquine is well-tolerated with a safe track record since 1955. The most common reported side effects include:

- headache, dizziness, ringing in your ears;
- nausea, vomiting, stomach pain;
- loss of appetite, weight loss;
- mood changes, feeling nervous or irritable;
- skin rash or itching; or
- hair loss.

GI side effects are minimized when taken with a meal or with milk. Antacid medications should be spaced apart by at least 4 hours.

Potential adverse effects by system, as listed on the FDA package insert:

- **Eye**: “Chloroquine retinopathy” is a rare side-effect of chronic use after multiple years of use. This has not occurred with <1 year of continuous use.

- **Dermatologic Reactions**: Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).

- **Hematologic Reactions**: Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, anemia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).

- **Gastrointestinal Reactions:** anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.

- **Cardiac Reactions:** Long-term use (>1 year) has been associated with the development of cardiomyopathy and arrhythmias. Specifically, chronic use has been associated with a mean +25msec prolongation of the QT interval after a median use of 3.5 years in patients with autoimmune diseases. In a 2018 review of short term antimalarial treatment trials (n=1076 with chloroquine), no serious cardiac adverse events were reported among 35,548 participants [14]

- **Allergic Reactions**: Urticaria, angioedema, and bronchospasm have been reported

- **Central Nervous System Reactions**: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, tinnitus, nystagmus, nerve deafness, convulsions, ataxia

- **Miscellaneous Reactions:** Weight loss, lassitude, exacerbation or precipitation of porphyria and non-light-sensitive psoriasis. Possible Hypoglycemia in persons with diabetes

On 24 April 2020, FDA issued a caution:

FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems

Close supervision is strongly recommended

"The FDA is aware of reports of serious heart rhythm problems in patients with COVID-19 treated with hydroxychloroquine or chloroquine, often in combination with azithromycin and other QT prolonging medicines. We are also aware of increased use of these medicines through outpatient prescriptions. Therefore, we would like to remind health care professionals and patients of the known risks associated with both hydroxychloroquine and chloroquine. We will continue to investigate risks associated with the use of hydroxychloroquine and chloroquine for COVID-19 and communicate publicly when we have more information."

"Hydroxychloroquine and chloroquine can cause abnormal heart rhythms such as QT interval prolongation and a dangerously rapid heart rate called ventricular tachycardia. These risks may increase when these medicines are combined with other medicines known to prolong the QT interval, including the antibiotic azithromycin, which is also being used in some COVID-19 patients without FDA approval for this condition. Patients who also have other health issues such as heart and kidney disease are likely to be at increased risk of these heart problems when receiving these medicines."

Mitigation of Risk: The inclusion / exclusion criteria exclude cardiac risk factors, chronic kidney disease, and anti-arrhythmia medicines. On 24 April, additional QT prolonging medicines are excluded.

2.3.2 Known Potential Benefits

- There are no known benefits in humans for preemptive treatment.
- *In vitro* antiviral activity against SARS-CoV and SARS-CoV2 viruses.
- Chloroquine and Hydroxychloroquine have a long history of safe, effective use as an antimalarial, both acutely and long-term use.
- Chloroquine is being used therapeutically for severe COVID-19 disease in China and Korea.
- Commonly used as a chronic medication for autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus).
- Recent studies have shown potential broad antiviral effects *in vitro* at dosages below currently recommended clinical dosing, reducing risk of potential adverse effects listed above.

3 OBJECTIVES

3.1 Study Objectives

To determine if hydroxychloroquine is effective at prevention of COVID-19 disease or reducing disease severity.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

Asymptomatic Cohort

- Incidence of COVID-19 disease within 14 days (among those asymptomatic at baseline)

Symptomatic Cohort

- Change in symptom severity score (visual analog scale 0-10) over 14 days

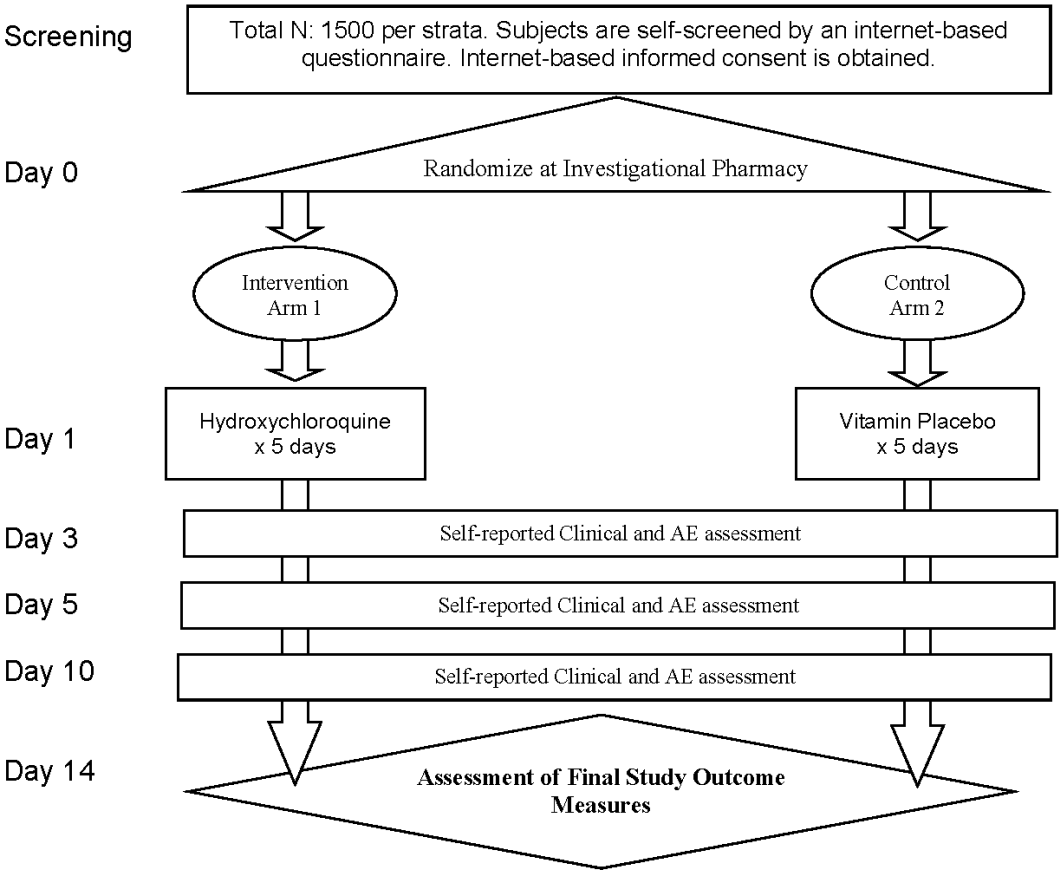
3.2.2 Secondary Outcome Measures

- Incidence of hospitalization or death
- Incidence of confirmed SARS-CoV-2 detection
- Incidence of symptoms compatible with COVID-19 (possible disease)
- Incidence of all-cause study medicine discontinuation or withdrawal
- Incidence of adverse reactions
- Symptom severity on day 5 or 14 via visual analog scale
- Ordinal Scale of COVID-19 Disease Severity at day 14 (among those who are symptomatic at trial entry)
  - Illness without hospitalization
  - Hospitalization (or post-hospital discharge)
  - Hospitalization with ICU stay or Death

Assessment of outcome measures will be primarily by self-report. As necessary, COVID19 disease will be verified from public health records, medical records, or death certificates. The primary endpoints are different for the two cohorts (those who are asymptomatic with known exposure; or those who are symptomatic at trial entry), and analyses will be done separately for the two cohorts.

The primary analysis will use PCR+ confirmed disease. However if the absence of sufficient testing supplies continues then outpatients will not be offered SARS-CoV-2 testing unless they are sick enough to be hospitalized. In that case an alternate a priori planned analysis will define incident COVID19 disease as a composite of SARS-CoV-2 PCR+ confirmed result OR symptomatic disease (i.e. possible) COVID-19 in those without testing.

4 STUDY DESIGN



If hospitalization occurs, this SAE will be followed for up to 90 days

There are two strata: 1) asymptomatic healthcare workers or household contacts exposed to COVID-19 (n=1500); 2) symptomatic COVID-19 disease (n=1500). Follow up will occur up to 90 days for those with symptomatic COVID-19 disease who become hospitalized.

4.1 DESIGN

Randomized, double-blind, placebo-controlled clinical trial, parallel design

- Intervention Arm: Hydroxychloroquine 800 mg orally once (4 tablets), followed in 6 to 8 hours by 600 mg (3 tabelts), then 600 mg once a day for 4 consecutive days (5 days in total)
- Control Arm: Vitamin Placebo 4 tablets orally once, followed in 6 to 8 hours by 3 tablets, then 3 tablets once a day for 4 consecutive days (5 days in total)

4.2 Study participant duration

- 14 days consisting of internet-based virtual visits
- For participants ill with COVID-19 disease who are hospitalized (an SAE), observational follow up will extend to up to 90 days to assess final outcome status of their SAE.
- Pregnant women have their fetal outcome assessed postpartum to exclude a teratogenic SAE.

4.3 Study procedures

- All procedures will consist of internet-based questionnaires completed by self-report.
- Informed consent is provided to access medical records to verify information, as necessary.
- Optional: blood spot will be collected at approximately day 14.
- Optional: daily cardiac monitoring with remote EKG reads of QTc interval.

4.4 Individually identifiable health information:

Name, date of birth, addresses, and phone number will be collected so as to prescribe study medication. Email addresses will be collected for communication. If participants are hospitalized, the hospitalization date will be collected.

4.5 Substudies (if applicable)

Additional sub-studies will undergo separate IRB approval, and these studies will involve separate informed consent. Consented participants will be queried as to if they wish to participate in future research.

1) Serology for Coronavirus Antibodies: New Participants will be offer an optional participation in self-collection of dried blood spots in order to measure serologies for antibodies. Participants who have already been consented and entered the trial, will be approached for amendment of consent. The purpose of serology testing is two-fold: First, to verify infection. Second, the prevalence of antibodies will be compared among symptomatic and asymptomatic persons with a scientific question of how many asymptomatic persons seroconvert after a high risk exposure in the absence of symptomatic illness. The exact serology methodology to be conducted will be determined, based on availability and diagnostic performance. Blood spot collection materials (e.g. 18g lancet, filter paper, bandaid, instructions, and return envelope). (Optional)

2) Cardiac Monitoring with handheld EKG to check cardiac QTc interval once daily for the first 7 days as a safety substudy. (Optional)

5 STUDY ENROLLMENT AND WITHDRAWAL

Participants will undergo screening via internet-based forms. The screening and inclusion criteria will be based on self-report.

5.1 Subject Inclusion Criteria

- Exposure to a COVID19 case within <=4 calendar days as either:
    - Occupational exposure (healthcare worker, first responder, etc.)
    - Household contact

  OR
- Symptomatic COVID-19 disease
    - Confirmed diagnosis with PCR+ SARS-CoV-2 within <=4 days of symptom onset OR
    - Individual with compatible symptoms with exposure to known PCR+ SARS-CoV-2 case within 14 days AND compatible symptoms of fever, cough, or shortness of breath (and no available /pending testing for the individual)*
- >= 18 years of age
- Provision of informed consent

5.2 Subject Exclusion Criteria

- Current Hospitalization
- Contraindication or allergy to hydroxychloroquine
- Retinal eye disease
- Concurrent malignancy requiring chemotherapy
- Known glucose-6 phosphate dehydrogenase (G-6-PD) deficiency
- Known chronic kidney disease, stage 4 or 5 or receiving dialysis
- Known Porphyria
- Weight < 50 kg
- Structural or ischemic heart disease
- Personal or Family history of prolonged QT
- Current use of: hydroxychloroquine, chloroquine, or cardiac medicines of: flecainide, Tambocor; amiodarone, Cordarone, Pacerone; digoxin or Digox, Digitek, Lanoxin; procainamide or Procan, Procanbid, propafenone, Rythmal; or sotalol.
- Current use of QT prolonging medicines of:
    - Antimicrobials: levofloxacin, ciprofloxacin, moxifloxacin, azithromycin, clarithromycin, erythromycin, ketoconazole, itraconazole, or mefloquine
    - Antidepressants: amitriptyline, citalopram, desipramine, escitalopram, imipramine, doxepin, fluoxetine, wellbutrin, or venlafaxine
    - Antipsychotic or mood stabilizers: haloperidol, droperidol, lithium, quetiapine, thioridazine, ziprasidone
    - Methadone
    - Sumatriptan, zolmitriptan

Rationale for inclusion / exclusion criteria:

* As of 20 March 2020, testing is limited in many U.S. states and locales due to insufficient supplies. Thus, outpatient testing may not be available. A person with known exposure to a confirmed COVID-19 case with subsequent compatible symptoms is eligible for enrollment, if testing is not available. If a symptomatic person tests negative for SARS-CoV-2, they are not eligible for enrollment.

Mean Incubation period is ~5.2 days, thus we wish to limit enrollment to those with a higher risk of progression and deliver study medicine in a time period to intervene to prevent disease or ameliorate disease (i.e. start of study medicine by <=4 days after exposure). The current (as of March 17, 2020) delays in testing makes this window particularly tight, and it may need to be relaxed in the future via protocol amendment.

In clinical practice of tropical medicine, chloroquine or hydroxychloroquine are prescribed without any baseline laboratory testing or monitoring.

Chronic use of hydroxychloroquine for >1 year can cause retinopathy or cardiomyopathy, thus persons with baseline conditions will be excluded. Study medicine is excreted via the kidney with dose reduction recommended in CrCl <30 cc/min (Stage 4 Kidney Disease). G-6-PD deficiency is listed as a caution on the FDA label. G-6-PD testing is not routinely performed in clinical care prior to giving hydroxychloroquine prescriptions (unlike with primaquine). Medication exclusions are for possible drug-drug interactions, particularly with cardiac arrhythmia medicines with a caution on the FDA-package insert.

On April 20, 2020, FDA mandated exclusion of structural or ischemic heart disease; or personal or family history of prolonged QT.

On April 24, 2020, FDA issued a caution for QT prolongation in persons with heart disease, chronic kidney disease, or taking other QT prolonging medicines.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

Participants will be randomized via permuted block randomization. Randomization will be recorded on an electronic log by the pharmacy. Study investigators and subjects will be blinded. There will be separate randomization schedules for the two cohorts (asymptomatic with exposure or symptomatic).

Masking Procedures

Participants will be provided masked study medicine, shipped by courier (e.g. FedEx). The intervention vs. placebo will not be identical; however, participants and outcome assessors will be masked to their assignment.

5.3.2 Reasons for Withdrawal

Participants may withdraw at any time point at their discretion.

5.3.3 Handling of Withdrawals

Withdraws will be counted as failures for the secondary endpoint of completion of study medication.

Participants who discontinue study medication will still be asked to complete the follow up visit schedule.

5.3.4 Termination of Study

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

- Unexpected, significant, or unacceptable risk to subjects
- Interim analyses by the DSMB.
- Insufficient compliance with protocol requirements
- Data are not sufficiently complete and/or not evaluable
- Regulatory authorities decide that study should be terminated

If the study is prematurely terminated for harm, current subjects will complete follow up, and no further subjects will be enrolled. If the study is terminated due to benefit, then the study will immediately convert into an open-label prospective cohort to collect further observational data on the safety and efficacy of the intervention, up to the IRB approved recruitment limit.

6 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

FDA-approved formulation of hydroxychloroquine will be purchased.

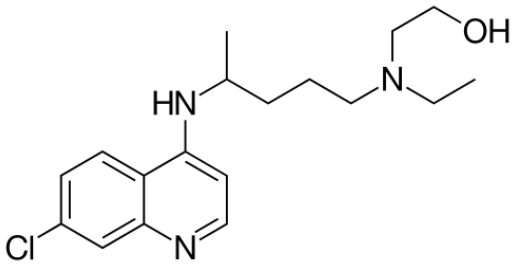
6.1.2 Formulation, Packaging, and Labeling

The study medicines will be packaged by the MHealth Investigational Drug Services. Dispensed medications will be delivered by courier (e.g. Fedex) to study participants.

Labels will include: “Caution: New Drug – Limited by Federal Law to investigational use. Keep out of reach of children.”

6.1.3 Drug Description:

Hydroxychloroquine sulfate



6.1.4 Formulation: 200mg tablet (= 155 mg base of chloroquine)

6.1.5 Pharmacokinetics:

- Absorption: Rapid and almost completely
- Distribution: Widely distributed into body tissues
- Metabolism: Partially hepatic to main metabolyte of desethylchloroquine
- Excretion: Urine (>=50% as unchanged drug); acidification of urine increases elimination
- C_{max} = 1.2 nmol/mL = 1.2 μmol/L = 1.2 μM at 400mg single dose.[15]
- T_{max} = 2.4 hours
- $T_{1/2}$ = 172 ± 39 hours = 7.1 +1.6 days
- AUC_{last} = 75.4 ± 47 nmol/h/mL
- This C_{max} is in the therapeutic window for SARS-COV2 activity.
- Steady state doses for 400mg dose is 974 μg/L = 2.24 μM [16], thus a 600mg dose should generate approximately 3.4 μM , which is above the EC50 of viral inhibition of 1.3 μM (EC50 = 50% inhibition; however, the more inhibition the better, likely).

Population PK parameter modeling: 5 day regimen

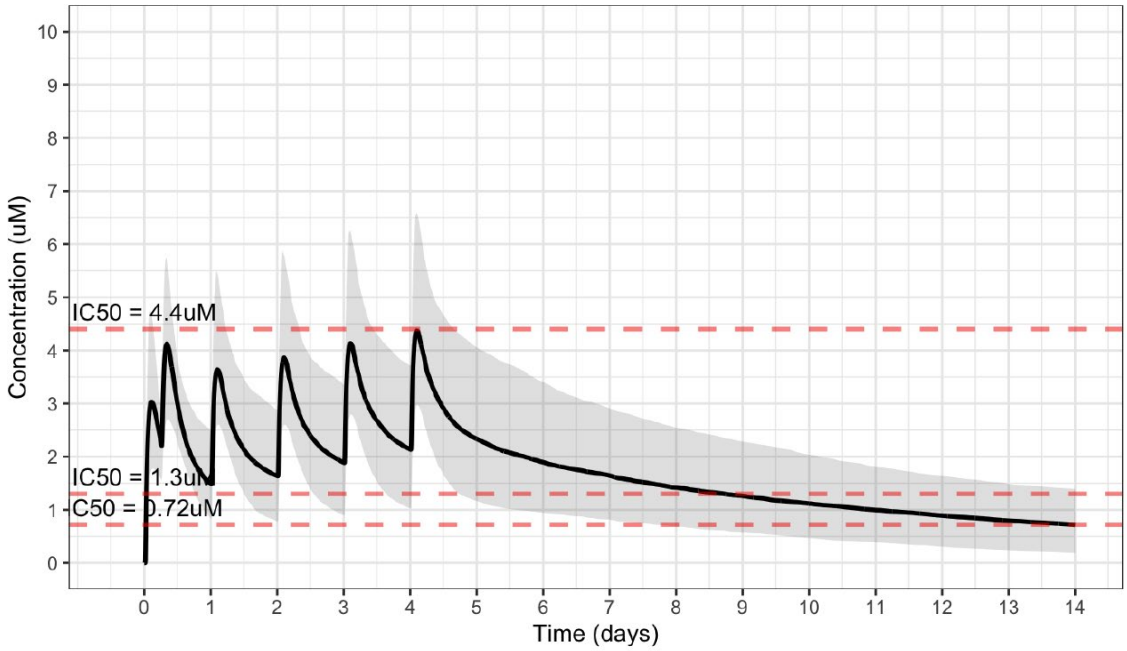
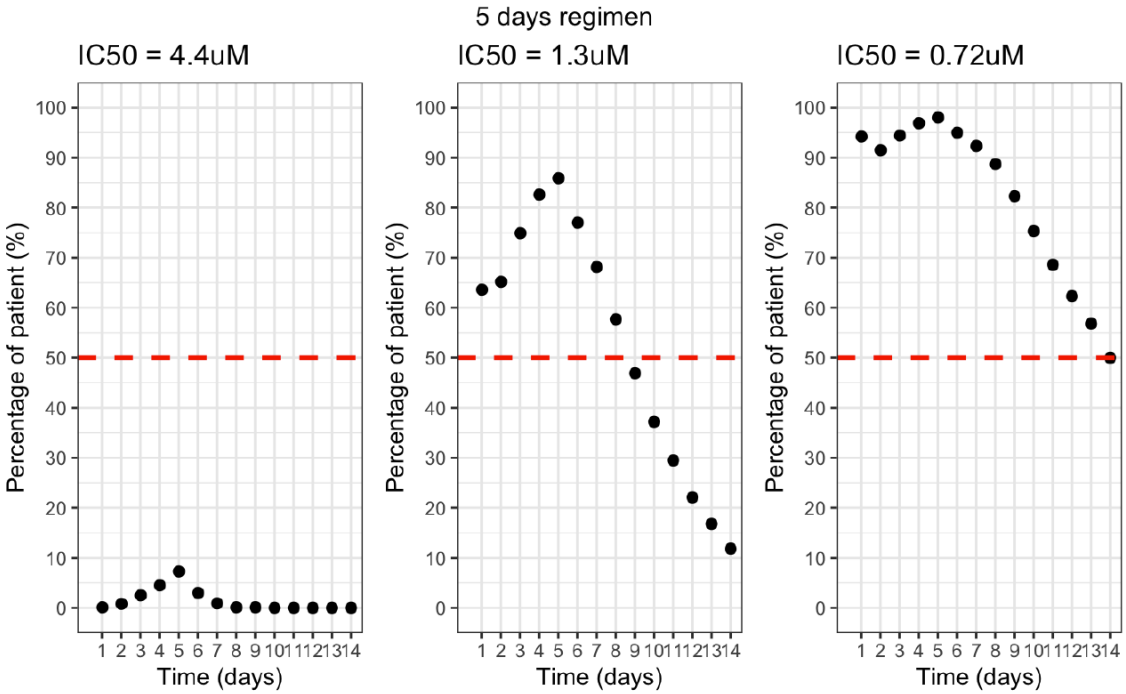


Figure courtesy of Dr. Mahmoud Al-Kofahi of College of Pharmacy, Univ. of Minnesota

The EC50 has been reported as 0.72 μM [5], although this is not a precise measurement, and should be view with a range of error present (but not reported). The EC50 is the point of 50% maximal inhibition, so more drug would be better (balanced against toxicity and drug supply). The percentage of persons achieving a 24 hour level above the EC50 is as follows (**Figure**).



6.1.6 Product Storage and Stability

Store at room up to 30° C (86° F). Dispense in a tight, light-resistant container.

6.2 Dosage, Preparation, and Administration of Investigational Product

Drug/Device Handling:

Hydroxychloroquine or placebo will be dispensed by the MHealth Investigational Drug Service (IDS) Pharmacy. To do so, study investigators will send a prescription to the IDS Pharmacy, the pharmacy will randomize the subject, and dispense the appropriate study medicine. The medicine will then be provided to research volunteers via FedEx / courier delivery in the United States.

6.3 Modification of Investigational Product for a Participant

With mild side effects, participants will be instructed to split the 3 tablet daily dosing into multiple times per day.

In the event of substantial side effects, participants may discontinue the study medication and stay in the study to complete follow up.

6.4 Accountability Procedures for the Investigational Product:

Accountability will be via self-report at the day 5 virtual visit.

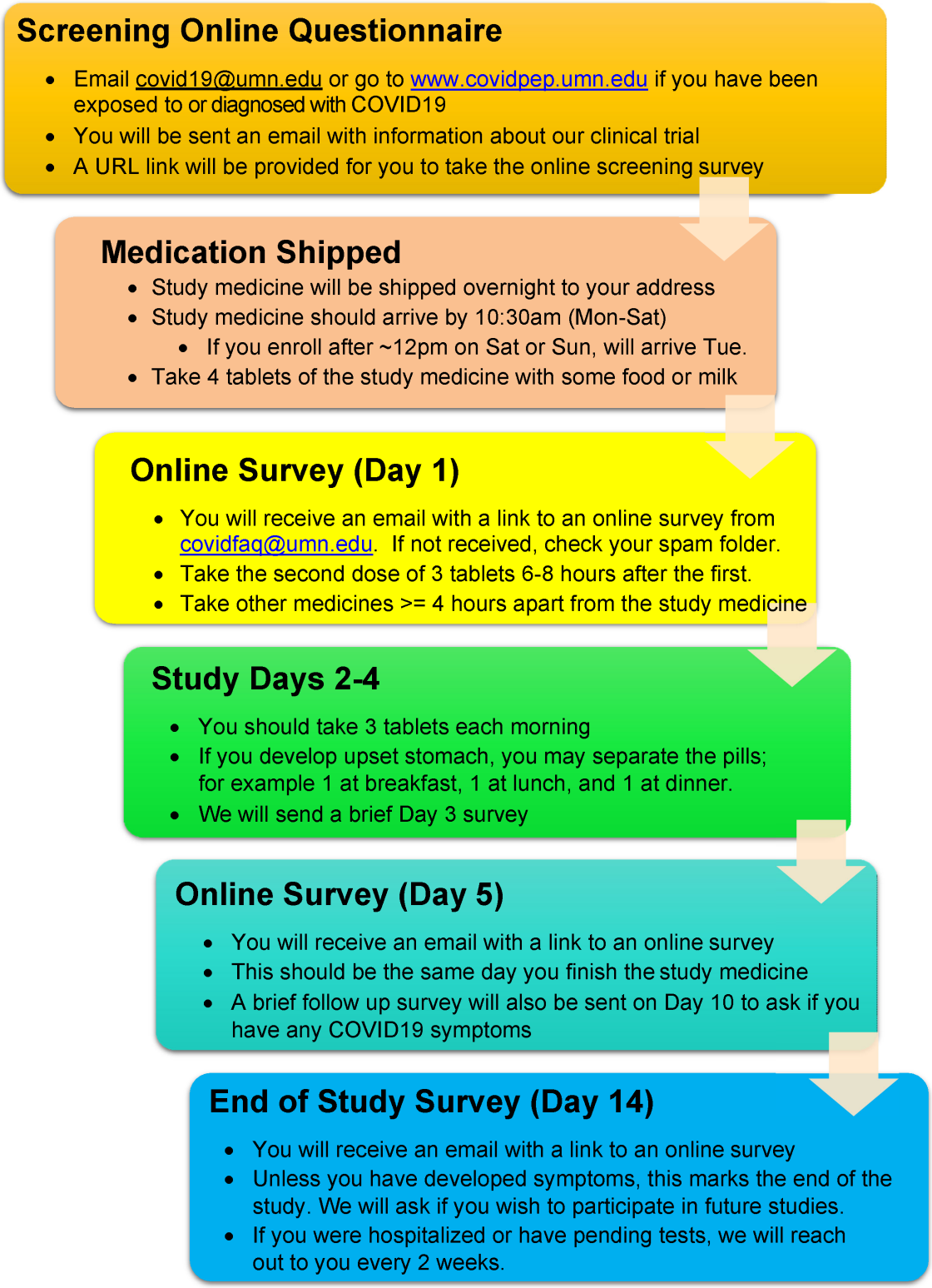
6.5 Assessment of Subject Compliance

Adherence will be via self-report at day 5 virtual visit.

6.6 Concomitant Medications/Treatments

Participants may receive other concomitant medications or therapies, and will be asked to report these in regards to other therapies received on day 1, day 14, and in the event of hospitalization.

7 STUDY SCHEDULE



7.1 Screening

- Baseline screening for eligibility
- Informed consent by self-administered
- This will be performed via a web-based form. Eligibility criteria will be by self-report.

7.2 Enrollment/Baseline

Randomization (Day 0)

- Participants will be randomized by a computer-generated algorithm using a permuted block randomization sequence.
- Randomization will be stratified by symptomatic vs. asymptomatic status at baseline.
- Investigational pharmacy will dispense the masked study medicine
- Study personnel will then FedEx study medicine to the participant
- Participant will be sent an email to expect medication to arrive by 10:30am

7.3 Follow-up

Day 1 Virtual visit

- Verify receipt of study medicine
- Clinical status check-in
    - Participant starts study medicine (4 tabs), then 3 tabs in 6-8 hours, then 3 tabs daily.
- Query for SARS-CoV-2 testing
- Query for symptom status (0-10 visual analog scale of symptom severity)
- Query for hospitalization or SAEs
- Query for medication-related side effects / AEs

Day 3 Virtual visit

- Query for symptom status (0-10 visual analog scale of symptom severity)
- Query for hospitalization or SAEs
- Query for medication-related side effects / AEs

Day 5 Virtual visit

- Query for symptom status (0-10 visual analog scale of symptom severity)
- Assessment of adherence by self-report
- Completion of study medicine, which has a ~7 day half-life
- Query for study medicine side effects since enrollment
- Query for SARS-CoV-2 testing
- Query for hospitalization or SAEs

Day 10 Virtual visit

- Query for symptom status (0-10 visual analog scale of symptom severity)
- Query for SARS-CoV-2 testing

- Query for SARS-CoV-2 testing
- Query for hospitalization or SAEs

7.4 Final Study Visit

- Day 14 Visit
    - Query for symptom status (0-10 visual analog scale of severity)
    - Query for study medicine side effects since enrollment
    - Query for SARS-CoV-2 testing
    - Query for hospitalization or SAEs
    - Query for pregnancy status
    - Final outcome assessment
    - Assess other medicines used during study period
    - Optional dried blood spot collection, return in pre-paid envelope.

    If participations have a SAE prior to the final study visit (e.g. hospitalization), the final resolution of the event will be followed until resolution or up to 90 days. The hospitalization eCRF will be sent in 14 days interval to assess clinical outcome / resolution of the hospitalization. Pregnancies will be followed through delivery to assess for any teratogenic SAE.

7.5 Early Termination Visit

If participants develop new / worsening symptoms of coronavirus, they will be directed to their healthcare provider and/or local public health authority for clinical care. We will follow up of hospitalized patients for resolution of their SAE for up to 90 days to assess their final outcome. Participants will be sent the Hospitalization eCRF 14 days after hospitalization is reported with repeats in 14 day intervals until the participant is discharged from the hospital.

7.6 Unscheduled / Sick Visit

Subjects will be provided a central email contact: faq.covid19@gmail.com as a contact point for questions or concerns. This email will forward to an on-call study physician who will call the participant to resolve their concerns.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

Clinical evaluations are by self-report.

8.2 Laboratory Evaluations

SARS-COV-2 positivity is by self-report. Informed consent asks for access to medical records.

Follow up PCR testing within 14 days is asked on followed questionnaires. Pending test results at 14 days or during hospitalization will be queried for final results with repeat survey sent at day 28.

Informed consent will request permission to contact local public health authorities or their medical provider in the event of lost to follow up or COVID19 disease.

There is no incentive to be dishonest, and we believe healthcare workers in particular will take their responsibilities seriously.

An optional dried blood spot collection will be offered at day 14. At time of informed consent, participants may opt into this collection. The dried blood spots will be used for future serology testing. Participants who opt into this testing will be mailed: i) instructions; ii) Whatman filter paper for dried blood spot collection; iii) one time use lancet; iv) return envelope.

Participants who have entered the trial prior to dried blood spot being offered and are <90 days from study entry will be contact with the option for dried blood spot testing of their antibody serology.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Hydroxychloroquine has a track record of safety since its FDA-approval in 1955. As an already, FDA-approved medicine, this trial is designed as a pragmatic trial in the setting of a public health emergency.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1 Adverse Events

Hydroxychloroquine has an excellent safety track record, being first FDA-approved in 1955. Adverse events will not be captured, unless they result in hospitalization. See Serious Adverse Events below.

Expected adverse events would include normal events within the general population as well COVID19-related disease events which may include need for hospitalization, pneumonia, respiratory failure, sepsis, and death.

9.2.2 Reactogenicity (for Vaccine Studies and Some Therapeutic Trials)

Not applicable

9.2.3 Serious Adverse Events (SAEs)

Hospitalization or death are protocol-defined endpoints.

SAEs (e.g. hospitalizations) will be followed for up to 90 days to assess final outcome.

9.2.4 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Not applicable

9.3 Reporting Procedures

9.3.1 Serious Adverse Events

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if it results in any of the following outcomes:

- Death
- Life-threatening adverse event (as below)
- Hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Congenital anomaly/birth defect.
- Important medical events that may not result in death, but are life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

    Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening adverse events: An AE is considered “life-threatening” if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death. For life threatening AEs, subjects would be recommended /expected to be hospitalized.

Based on the known safety track record of hydroxychloroquine, this pragmatic protocol will focus on death, life-threatening AEs, and hospitalizations. Incapacity / permanent disability is a possibility with COVID19, but this is not associated with hydroxychloroquine. In the event of incapacity, the subject would be expected to be hospitalized.

Hydroxychloroquine and chloroquine are not known to cause teratogenic events and are viewed as safe in pregnancy, especially with short term use. With this trial’s sample size, this will not further delineate this risk. COVID19 disease may indeed be teratogenic. For women who are pregnant, we will ask to follow them through the end of their pregnancy, and they will be sent a follow up eCRF at 1 month post-partum based on their reported estimated date of delivery as provided at the day 14 study visit.

Thus, the hospitalization or death secondary endpoint will capture relevant SAEs. For those with ongoing hospitalization at the day 14 study visit, participants will be queried in 14 day intervals with the hospital eCRF to assess their final clinical outcome.

9.3.2 Regulatory Reporting

As hydroxychloroquine is an FDA-approved medicine being used at standard dosing, reporting to regulatory authorities will occur in summary format after each DSMB reports and at a frequency of at least annually.

Serious unexpected suspected adverse reactions (SUSARs) which are not expected with COVID-19 nor listed in the FDA package insert will be reported to the IRB. Those SUSARS which are deemed by an independent medical monitor to be related to the study medicine will be reported to the FDA and IRB.

9.3.3 Reporting of Pregnancy

Chloroquine and hydroxychloroquine are not known to be teratogenic. Chloroquine and hydroxychloroquine can accumulate in neonatal eyes. Conversely, the risk of severe COVID-19 infection is unknown, but likely is a heightened risk in pregnant women. The CDC states, “We do not have information on adverse pregnancy outcomes in pregnant women with COVID-19. Pregnancy loss, including miscarriage and stillbirth, has been observed in cases of infection with other related coronaviruses (SARS-CoV and MERS-CoV) during pregnancy. High fevers during the first trimester of pregnancy can increase the risk of certain birth defects.”

Thus, the risk/benefit would favor the enrollment of women who may be or are pregnant, so as to not discriminate against pregnant women.

For women who are pregnant, we will ask to have follow through the end of their pregnancy to assess outcome of the pregnancy via a brief survey.

9.4 Type and Duration of Follow-up of Subjects after Adverse Events

Participants who are hospitalized for COVID-19 or SAEs will have up to 90 day follow up conducted to assess their final outcome. Management will be as per the participant’s local healthcare provider.

9.5 Safety Oversight (DSMB)

A data and safety monitoring board (DSMB) will oversee the trial. The quorum will include three members and a biostatistician. The PI will be a non-voting observer, providing input as requested. See the DSMB charter for more details.

10 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected and that the reported trial data are accurate, complete, and verifiable. Clinical monitoring also ensures that conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and Sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions. Monitoring will be the responsibility of the University of Minnesota.

The automated logic of the REDCap database system will enable complete records. All data are by self report.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

We hypothesize that hydroxychloroquine is superior to placebo for preventing progression to COVID-19 disease among those who are asymptomatic.

We hypothesize that hydroxychloroquine is superior to placebo for preventing progression among those with symptomatic mild COVID19 disease preventing hospitalization/death.

11.2 Sample Size Considerations

Two cohorts of 1500 subjects each:

1) Asymptomatic persons exposed to COVID-19 disease (750 in placebo, 750 in intervention);

2) Symptomatic outpatient COVID-19 disease (750 in placebo, 750 in intervention).

Assuming 90% power, a two-sided alpha = 0.05 and loss to follow-up up to 20%, for each cohort the planned sample size is 750 participants per arm based on the following assumptions:

- 10% transmission rate from COVID-19 cases to close contacts
- For those with symptomatic illness the proportions at day 14 in the placebo group are 90%, 8% and 2%, respectively for illness without hospitalization, hospitalization with ICU stay or death, and hospitalization with an ICU stay or death.

The estimated transmission rates are uncertain. Table 1 below (for the asymptomatic cohort with exposure) shows that we are well powered to detect even a smaller (40%) relative reduction in the incidence of COVID 19 with 80% power for transmission rates of at least 10% with placebo. Table 2 (for the symptomatic group) shows that we are well powered to detect a common odds ratio of 0.6-0.75 under the assumption that the control proportions for illness without hospitalization, hospitalization without ICU stay or death and hospitalization with ICU stay or death are 90%, 8% and 2%, respectively.

Table 1. Sample Size Table for Asymptomatic Participants (Healthcare worker or household contact) With Exposure

Estimated transmission rate with placebo	Estimated transmission rate with drug	Percent relative reduction in transmission rate	Sample size (per arm) with 90% power	Sample size (per arm) with 80% power
10%	5%	50%	621	474
	6%	40%	1014	771
12%	6%	50%	509	389
	7.2%	40%	831	632
15%	7.5%	50%	398	304
	9%	40%	648	493

Table 2. Sample size table for participants with symptomatic disease, assuming that the control proportions are 90% illness with no hospitalization, 8% hospitalization with no ICU stay or death and 2% hospitalization with ICU stay or death.

Log Odds Ratio	Odds Ratio	Sample size (per group) with 90% power	Sample size (per group) with 80% power
0.60	1.82	805	601
0.65	1.91	697	521
0.70	2.01	610	456
0.75	2.12	539	403

11.3 Planned Interim Analyses

A Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be provided at each DSMB report for the primary outcome for each cohort The O'Brien-Fleming boundaries will be truncated at alpha = 0.001 ($|Z| > 3.09$). For each cohort, interim analyses are separately planned at 25%, 50% and 75% of trial enrollment.

As enrollment may be brisk, the timing of interim analyses may be altered at PI discretion based on that pace of enrollment. It may be possible that the trial is fully enrolled by the time day 14 outcomes are available for the first 25% enrolled. In this case, any further analyses would be related as to when to release interim results.

At the first DSMB review, the stopping boundary is unlikely to be crossed. The purpose of this early review will assess the trends for safety/efficacy and allow for the DSMB to determine the probable timing of further reviews based on the pace of enrollment.

Should a stopping boundary be crossed, we would recommend an analysis to determine whether the findings are consistent across secondary endpoints, such that a clear answer is achieved. Starting with the 2nd DSMB review (at approximately 50% enrollment) the DSMB will be given the conditional power for both cohorts under both the study design parameters and the current data. If the conditional power is less than 20% then trial discontinuation may be considered.

In the event of early halting due to efficacy of the intervention, the study will immediately convert to an open label observational cohort of hydroxychloroquine prescribed to all consented participants in the relevant cohort.

In the event of early halting due to futility of no effect, a protocol modification will be made to alter the intervention.

Based on the public health situation, the DSMB has the prerogative to alter the stopping rules.

Sample Size Re-estimation:

At time of ~50% enrollment, a sample size re-estimation should occur based on the disease transmission rate in the control group. The *a priori* assumption (based on limited data) is 10% transmission risk. The new sample size estimation will take into account the updated transmission rate with no treatment and will be powered to detect a 50% relative reduction in outcome.

11.4 Final Analysis Plan

Primary outcome analyses (intention to treat):

Asymptomatic Cohort Primary Analysis:

Those with asymptomatic exposure: Incidence of COVID 19 disease by day 14 will be assessed via Fisher's Exact Test.

Symptomatic Cohort Primary Analysis:

Those with symptomatic disease at study entry: For a summary metric of the change in symptom severity over 14 days, a longitudinal change over time repeated measures mixed-regression model will estimate the treatment effect by study arm. Subjects without symptoms are coded as a zero severity. Persons hospitalized or dead are coded as 10 severity.

Participants who become symptomatic with COVID19 on Day 1 before receiving the study medicine will be described with the symptomatic cohort.

Secondary Analyses:

For the asymptomatic with exposure cohort, the primary analysis (intention to treat) will be repeated for participants who received at least one dose of the study medicine.

- Secondary endpoints will be assessed via Fisher's Exact test and median (with interquartile ranges) as appropriate.
- Those with symptomatic disease at study entry: Proportional odds models will be used to assess the ordinal scale for disease severity at day 14 (illness without hospitalization, hospitalization without ICU stay or death, or hospitalization with ICU stay or death).
- Severity of overall symptoms at Day 0, 1, 5, and 14 is recorded on a 0-10 visual analog scale. Severity of symptoms at Day 5 will be compared first as a categorical analysis (no symptoms vs. symptoms) via Fisher's Exact Chi Square.
    - Second among those with symptoms, the 0-10 visual analog scale severity data will be compared via independent two-sample *t* test. If data are non-normally distributed, then data will be compared via Mann-Whitney U by study arm.

A priori subgroup analyses will include assessment by:

- Confirmed SARS-CoV-2 disease or disease exposure
- Healthcare worker vs. Household contact
- Days from Exposure
- Decile of age
- Sex as a biological variable
- Censored subjects, who became symptomatic before receipt of the first dose of study medicine on D#1, will be separately analyzed and reported.

Handling of withdrawn subjects.

If there is a large lost to follow up / study discontinue rate, then the primary endpoint for the asymptomatic cohort would have a secondary analysis to assess incidence as a 3-category analysis of: i) no disease, ii) incident disease, or iii) unknown.

Similarly, the symptomatic cohort would add a fourth category of unknown.

Participants who stop taking the study medicine but who agree to be followed for 14 days will be assessed as intent-to-treat. On Day 14, we will ask for other medications or vitamins that were taken during the study period.

Screened Persons

Persons who are screened but not enrolled will be summarized in CONSORT diagrams and other descriptive summaries of their COVID-19 related information – with all data de-identified.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA

Source documents will include internet forms self-completed by participants directly entered into a RedCAP database.

This protocol is based on self-report.

This internet-based protocol is meant to enable a large number of participants to be recruited, quickly as well as maintain the safety of the research staff. In person visits, create a public health

Participants will be asked to provide consent to obtain medical records from their healthcare provider or public health official, if there is the need to verify outcomes – for SARS-CoV-2 test results or hospitalizations.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Study medications will be commercially procured U.S. FDA-approved hydroxychloroquine or under ANDA #210959 following Good Manufacturing Practice.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization guidelines), Declaration of Helsinki, and International Ethical Guidelines for Biomedical Research Involving Human Subjects, applicable U.S. government regulations and institutional research policies and procedures. All investigators must have received human subject protection and GCP training prior to human subject involvement.

14.2 Institutional Review Board

Prior to the initiation of the study, the protocol, all informed consent forms and the participant Information materials will be submitted to and approved by the single IRB of record. Likewise, any future amendments to the study protocol will be submitted and approved by the IRB before implementation. This protocol and any amendments will undergo review and approval by the Human Subjects Board at the University of Minnesota under DHHS Assurance FWA00000312.

14.3 Informed Consent Process

- Written informed consent will be obtained via an English-language, internet-based web form. If potential participants have questions, they may contact faq.covid19@gmail.com to reach a study staff member to answer their questions about research, either via email or a phone call.
- After completion of reading the form, participants will be assessed for comprehension, querying:
    - Concept of Randomization to hydroxychloroquine or vitamin placebo
    - Whether hydroxychloroquine is known to be effective in preventing disease
    - Duration of the study? (14 days)
    - Duration of taking the study medicine (5 days)
    - When follow up surveys will be sent (Days 1, 3, 5, 10 and 14)
    - If hydroxychloroquine can be shared? (No)

14.3.1 Informed Consent/Assent Process (in Case of a Minor)

- Persons under 18 years of age are not eligible to participate. COVID19 has negligible mortality in children <10 years, and rate of progression to symptomatic disease may likely be different. Furthermore, pediatric dosing is weight based, making remote administration more complicated with fixed dose 200mg tablets.

14.4 Exclusion of Women, Minorities, and Children

- Persons under 18 years of age are not eligible to participate. COVID19 has 0% mortality in children and young adults.
- Non-English speaking adults are not eligible as the webpage and consents will only be available in English.

14.5 Subject Confidentiality

- Interaction will be via internet-based RedCAP ECRFs conforming to required U.S. privacy and server security standards.
- Clinical data will be entered into a study specific database by designated staff on a regular basis from completed electronic Case Record Forms (eCRF). Access to database will be given to authorized personnel only (members of the immediate study team). eCRF and trial documents will be kept in a secure database.
- Documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the participant except as necessary for monitoring by the IRB or public health authorities
- No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.

14.6 Future Use of Stored Specimens

- No specimens are to be stored for future research.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Management Responsibilities

Investigators will maintain a REDCAP database of study records.

Survey forms will be self-completed by study participants.

15.2 Data Capture Methods

- Data will be obtained via internet-based REDCAP forms.

15.3 Types of Data

- Participants will be asked to provide data regarding COVID19 exposure timing and location. They will also be asked to provide ongoing symptom reports during the follow-up period.

15.4 Timing/Reports

- An enrollment progress report will be generated monthly
    - Participants Enrolled
    - Participants on study
    - Participants completed the study
    - Lost to Follow Up
    - Cumulative COVID19 (pooled, both arms)
    - Cumulative Hospitalizations (pooled, both arms)
- A data safety monitoring board (DSMB) will review data after every 100 participants complete 14 days of follow-up.
- De-identified data will be shared with the research team members for analysis.

15.5 Study Records Retention

- No paper documents will be retained or stored.
- Digital records will be kept in a secure server setting.

15.6 Protocol Deviations

Protocol violations will be reported to the IRB of record.

16 PUBLICATION POLICY

Publication will be expeditiously made with a full, de-identified data made available.

17 LITERATURE REFERENCES

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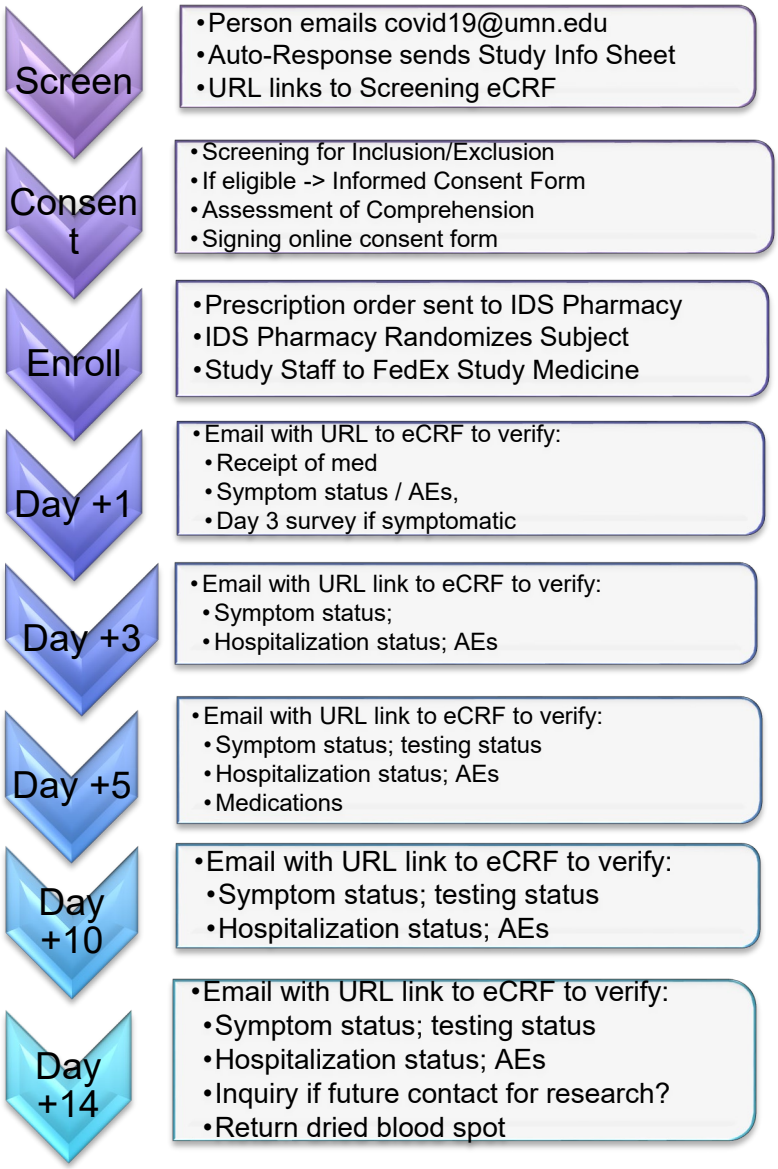
SUPPLEMENTS / APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Overview of Procedures



Participants with ongoing SAE / hospitalization at day 14 will be followed until hospital discharge or up to day 90 for final resolution.

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Version	Date	Protocol Changes
1.0	17 March 2020	Original Protocol
2.0	20 March 2020	• Enrollment window expanded from 3 days to 4 days. • Addition of Day 3 and 10 visits for persons who become symptomatic • Wording Separation of the co-primary endpoints of the two companion trials into two distinct primary endpoints (one for each trial). • Clarifications, better visual layout of some protocol sections
2.1	26 March 2020	• Day 10 visit changed to be universally implemented (by timing this was implemented, such that all participants received this visit)
2.2	27 March 2020	• Clarification on withdrawal (i.e. participants can stop study medicine but are asked to continue follow up). • Added chloroquine to exclusion medicines • FDA requested wording added to consent
2.3	24 April 2020	• Exclusion of QT-prolongation medications, personal or family history of QT syndrome, or structural heart disease • Addition of the April 24, 2020 FDA caution into consent form and stated efforts to mitigate risk for participants. • Change in symptomatic cohort primary endpoint to be change in symptom severity score over 14 days (does not effect post-exposure prophylaxis). • Removal of secondary endpoints of duration of hospitalization and cumulative time to PCR negativity among those positive. • Day 3 visits added for all for further safety monitoring. • Addition of optional cardiac monitoring • Addition of optional serology collection

Post-exposure Prophylaxis or Preemptive Therapy for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial

Statistical Analysis Plan

06 May 2020

Protocol Version, Date	Primary Endpoint
Protocol Version 1.0, March 17, 2020	Incidence of COVID19*
Protocol Version 2.0; March 20, 2020	Incidence of COVID19
Protocol Version 2.1, March 26, 2020	Incidence of COVID19
Protocol Version 2.2; March 27, 2020	Incidence of COVID19
Protocol Version 2.3, April 24, 2020	Incidence of COVID19

* Incidence of COVID19 disease, defined on March 17 and thereafter as: "The primary analysis will use PCR+ confirmed disease. However if the absence of sufficient testing supplies continues then outpatients will not be offered SARS-CoV-2 testing unless they are sick enough to be hospitalized. In that case an alternate a priori planned analysis will define incident COVID19 disease as a composite of SARS-CoV-2 PCR+ confirmed result OR symptomatic disease (i.e. possible) COVID-19 in those without testing."

I. Prophylaxis study primary outcome

a. The primary outcome will be presented for the treatment and control groups as proportions, and compared with Fisher's Exact tests.

b. The primary outcome will be presented for subgroups formed by contact type (household contact and healthcare workers), age groups (18-35, 36-50 and > 50), sex, and days from exposure. These are apriori subgroups defined in the Version 1.0 of the protocol.

c. Participants who are randomized into the prevention trial, but who become symptomatic on Day 1 before receiving the study medicine will be censored from the prevention cohort and analyzed with the companion treatment cohort.

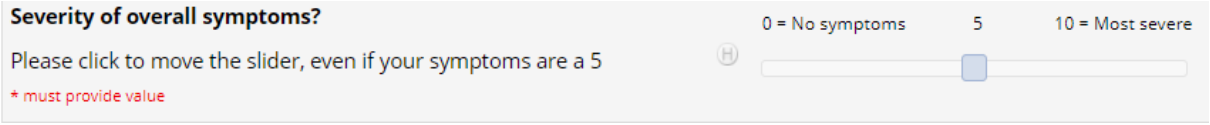
d. The primary outcome will be presented by subgroups formed by COVID test results (confirmed positive vs. other), age groups (18-35, 36-50, > 50), sex, and days from exposure onset to entry. These are apriori subgroups defined in the Version 1.0 of the protocol.

e. Medication adherence is captured on study day 5. Another subgroup of interest is comparing the treatment groups for change in symptom severity score after day 5 by adherence reported at day 5 (<= 75% versus > 75%).

II. Secondary outcomes

a. Secondary outcomes for incidence will be presented as proportions and compared between the treatment groups with Fisher's Exact tests.
b. Symptom severity scores were recorded with the online participant surveys at days 3, 5, 10 and 14 only for those who responded "yes" to "Any symptoms experienced".

i. Visual analog scale (0-10) for “overall symptom severity” is collected via a digital slider bar, which is marked with “0 = no symptoms”; 5 (placed in the middle); and “10 = severe symptoms”



ii. For those who responded “no” to “Any symptoms experienced” the symptom severity score for that visit is assigned as zero.

iii. For those hospitalized or with deaths, their symptom severity was scored as 10 if they did not respond to the visit survey.

iv. Analysis is by Kruskall Wallis tests among those with symptoms at day 14.

Clarifications (24 May 2020):

- Participants with missing outcome data are still included in the denominator, as the trial is performed as an intent to treat analysis.
- Sensitivity analyses were performed excluding participants with missing data from the denominator as well as including participants with missing data as events.